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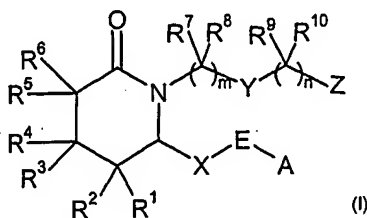
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ance Notes on Codes and Abbreviations" appearing at the begin-
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(54) Title: 2-PIPERIDONE DERIVATIVES AS PROSTAGLANDIN AGONISTS



(57) Abstract: The invention provides compounds of the Formula (I); wherein m, n, A, X, Y, Z, R1, R2, R4, R6, R7, R8, R9 and R10 are as defined in the description and claims, and pharmaceutically acceptable salts, solvates, pro-drugs, single isomers or racemic or non-racemic mixture of isomers thereof. The invention also provides methods for preparing, compositions comprising, and methods for using compounds of formula I.

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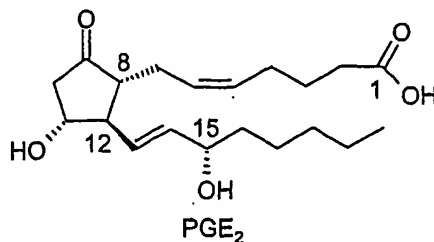
2-PIPERIDONE DERIVATIVES AS PROSTAGLANDIN AGONISTS

[0001] This invention relates to certain 2-pyrrolidone derivatives, and associated pharmaceutical compositions, methods for use as selective prostaglandin EP4 agonists, and methods of preparation thereof.

[0002] There are many references in the literature to prostaglandins or prostanoids (PGs), a term which is generic to natural and synthetic prostaglandins and prostaglandin-like compounds, and it is well known that even slight differences in their chemical structures or stereochemical configurations will have profound effects on their biological activity.

[0003] Prostaglandins or prostanoids (PGs) are a group of bioactive compounds derived from membrane phospholipids, and are formed from 20-carbon essential fatty acids and contain a cyclopentane ring. They fall into several main classes designated by letters and are distinguished by substitutions to the cyclopentane ring. The main classes are further subdivided by subscripts 1, 2, or 3 which reflect their fatty acid precursors.

[0004] An example of a particular species of the prostaglandin E is PGE₂, with the following structure:



[0005] At present four different receptor subtypes of PGE₂ are known and they are designated EP1, EP2, EP3, and EP4.

[0006] Uses for compounds possessing a strong binding activity to PGE₂ receptors comprise the prevention and /or treatment of immunological diseases (autoimmune diseases, organ transplantation, etc.), asthma, abnormal bone formation, neuronal cell death, thrombosis and stroke, hepatopathy, abortion, male and female sexual

dysfunction, premature birth, inflammation such as rheumatoid arthritis or retina neuropathy disorders such as glaucoma.

[0007] Prostaglandins and their associated receptors are more fully described in for example: M. Abramovitz et al., The Utilization of Recombinant Prostanoid Receptors to Determine the Affinities and Selectivities of Prostaglandins and Related Analogs, Biochimica et Biophysica Acta 2000, 1483, 285-293.

[0008] The involvement of prostaglandin E receptor agonists in bone resorption is described in, e.g., T. Suzawa et al., The Role of Prostaglandin E Receptor Subtypes in Bone Resorption: An Analysis Using Specific Agonists for the Respective EPs, Endocrinology 2000, 141, 1554-1559; K. Ono et al., Important Role of EP4, a Subtype of Prostaglandin (PG) E Receptor, in Osteoclast-like Cell Formation from Mouse Bone Marrow Cells Induced by PGE2, J. of Endocrinology 1998, 158, R1-R5; M. Suda et al., Prostaglandin E Receptor Subtypes in Mouse Osteoblastic Cell Line, Endocrinology 1996, 137, 1698-1705.

[0009] These selective prostaglandin E receptor agonists are also useful for the treatment of gastric lesions, see e.g. H. Araki, et al. The Roles of Prostaglandin E Receptor Subtypes in the Cytoprotective Action of Prostaglandin E2 in Rat Stomach, Aliment. Pharmacol. Ther. 2000, 14 (Suppl. 1), 116-124; T. Kunikata, et al., E Type Prostaglandin Inhibits Indomethacin-Induced Small Intestinal Lesions Through EP3 and EP4 Receptors: A Study Using Rats and Knockout Mice, Gastroenterology 118, abstract #3787.

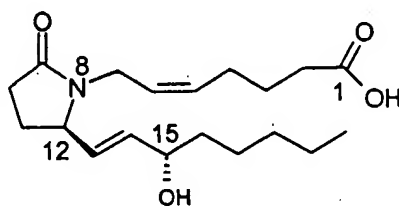
[00010] Other uses of prostaglandin E receptor agonists are for improvement of kidney function as described in, e.g., M. D. Breyer, et al, Prostaglandin E Receptors and the Kidney, Am. J. Physiol. 2000, 279, F12-F23, and K. E. Purdy, et al., EP1 and EP4 Receptors Mediate Prostaglandin E2 Actions in the Microcirculation of Rat Kidney, Am. J. Physiol. 2000, 279, F755-F764; for thrombosis and stroke as well as for other conditions where an inhibition of platelet aggregation would be beneficial as described in, e.g., B. Z. S. Paul, et al, Distribution of Prostaglandin IP and EP Receptor Subtypes and Isoforms in Platelets and Human Umbilical Artery Smooth Muscle Cells, Br. J. Haematol. 1998, 102, 1204-1211; for antiinflammatory effects through inhibition of TNF-alpha generation as described in, e.g. K. K. Meja, et al. Characterization of prostanoid receptor(s) on human blood monocytes at which prostaglandin E2 inhibits lipopolysaccharide-induced tumor necrosis factor-alpha generation, Br. J. Pharmacol. 1997, 122, 149-157, and A. Eigler, et al. Anti-inflammatory activities of cAMP-elevating agents: enhancement of IL-10 synthesis and concurrent suppression of TNF production, J. Leukoc. Biol. 1998, 63, 101-107; or

for glaucoma as described in, e.g., M. Takamatsu, et al. Localization of Prostaglandin E Receptor Subtypes in The Ciliary Body of Mouse Eye, Exp. Eye Res. 2000, 70, 623-628, and D. F. Woodward, et al, Molecular Characterization and Ocular Hypotensive Properties of the Prostanoid EP2 Receptor, J. Ocul. Pharmacol. Ther. 1995, 11, 447.

5 [00011] Treatment of impotence and/or erectile dysfunction by using prostaglandins that are selective EP2 and/or EP4 receptor ligands have been disclosed in International Application Publication No. WO 99/02164 assigned to Pharmacia & Upjohn AB.

10 [00012] Additional information relating to prostaglandins and their receptors is described in Goodman & Gillman's, The Pharmacological Basis of Therapeutics, ninth edition, McGraw-Hill, New York, 1996, Chapter 26, pages 601-616.

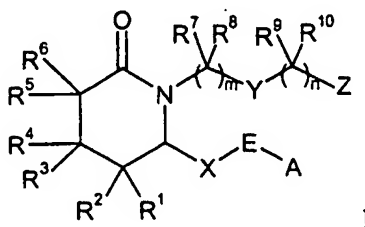
[00013] 8-Aza-11-deoxy-prostaglandin analogs corresponding to PGE2 would have the following structure:



8-Aza-11-deoxy-prostaglandin

15 [00014] Substitution of a nitrogen for the carbon at C-8 causes a change in the three dimensional conformation of the resultant prostaglandin, and because structure is related to biological activity, such a conformational change will have a significant effect upon the biological activity. 8-Aza-11-deoxy prostaglandin E's with the natural
20 side chains have been reported in the literature, see e.g. BE 841,165, assigned to Syntex USA, Inc.

[00015] This invention relates to compounds represented by Formula I:



wherein:

m is from 1 to 4;

n is from 0 to 4;

5 A is alkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, cycloalkylalkyl, or aryloxyalkyl;

E is -CHOH- or -C(O)-;

X is -(CH₂)₂- or -CH=CH-;

Y is, -CH₂-, arylene, heteroarylene, -CH=CH-, -O-, -S(O)_p- where p is from 0 to 2,
or -NR_a- where R_a is hydrogen or alkyl;

10 Z is -CH₂OH-, -CHO, tetrazol-5-yl, or -COOR_b where R_b is hydrogen or alkyl; and
R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ each independently are hydrogen or
alkyl; or a pharmaceutically acceptable salt or solvate, prodrug, single isomer or
racemic or non-racemic mixture of isomers thereof.

[00016] The subject compounds have high selectivity in their EP4 receptor agonist
15 activity. The increase in selectivity would alleviate the severe side effects frequently
observed following administration of non-selective prostaglandin agonists. Therefore
compounds of this invention are desirable.

[00017] In another aspect the invention relates to pharmaceutical compositions
containing a therapeutically effective amount of at least one compound of Formula I
20 or its pharmaceutically acceptable salt or solvate, prodrug, single isomer or racemic
or non-racemic mixture of isomers in admixture with at least one suitable carrier,
diluent or excipient.

[00018] In another aspect the invention provides a method of treatment of a disease, in
particular a bone disease, in a mammal treatable by administration of a prostaglandin
25 EP4 receptor agonist, comprising administration of a therapeutically effective amount
of a compound of Formula I or its pharmaceutically acceptable salt.

[00019] In another aspect the invention provides a process for preparing compounds of
Formula I.

[00020] Unless otherwise stated, the following terms used in the specification and claims
30 have the meanings given below:

[00021] "Alkoxy" means a radical OR where R is an alkyl as defined herein e.g., methoxy, ethoxy, propoxy, butoxy and the like.

[00022] "Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2 propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and the like.

[00023] "Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g., methylene, ethylene, 2,2-dimethylethylene, propylene, 2 methylpropylene, butylene, pentylene, and the like.

[00024] "Alkylthio" means a radical SR where R is an alkyl as defined above e.g., methylthio, ethylthio, propylthio, butylthio, and the like.

[00025] "Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon radical which is optionally substituted independently from each other with one or more substituents, preferably one, two, or three, selected from the group consisting of alkyl, haloalkyl, halo, nitro, cyano, amino, methylenedioxy, ethylenedioxy, optionally substituted phenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl -V-OR', -V-NR'R", -V-C(O)-R', -V-S(O)O-2-R'; -V-N-SO2-R', -V-SO2-NR'R", -V-N-C(O)-NR'R", where V is a bond or a C1-C3 alkylene group, and R' and R" are each independently from each other hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, optionally substituted phenyl, heteroaryl, cycloalkyl, or heterocyclyl. More specifically the term aryl includes, but is not limited to, phenyl, chlorophenyl, methoxyphenyl, methoxymethylphenyl, phenyloxyphenyl, 1-naphthyl, 2-naphthyl, and the derivatives thereof.

[00026] "Arylene" means a divalent monocyclic or bicyclic aromatic hydrocarbon radical and includes divalent versions of the aryl radicals described above.

[00027] "Arylalkyl" and "Aralkyl", which may be used interchangeably, mean a radical -RaRb where Ra is an alkylene group and Rb is an aryl group as defined herein; e.g., benzyl, phenylethyl, 3-(3-chlorophenyl)-2-methylpentyl, and the like are examples of arylalkyl.

[00028] "Arylcylcoalkyl" means a radical -RaRb wherein Ra is cycloalkylene as defined herein and Rb is aryl as defined herein.

[00029] "Aryloxy" means a radical -ORa wherein Ra is aryl as defined herein.

5 [00030] "Aryloxyalkyl" means a radical -RaRb wherein -Ra is alkylene as defined herein and Rb is aryloxy as defined herein.

[00031] "Cycloalkyl" means a monovalent saturated carbocyclic moiety consisting of mono- or bicyclic rings. Cycloalkyl can optionally be substituted with one or more substituents, wherein each substituent is independently hydroxy, alkyl, alkoxy, halo, haloalkyl, amino, monoalkylamino, or dialkylamino, unless otherwise specifically indicated. Examples of cycloalkyl moieties include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like, including partially unsaturated derivatives thereof.

[00032] "Cycloalkylene" means a divalent saturated carbocyclic moiety consisting of mono- or bicyclic rings, including divalent versions of the cycloalkyls noted above.

15 [00033] "Cycloalkylalkyl" means a moiety of the formula -R'-R", where R' is alkylene and R" is cycloalkyl as defined herein.

[00034] "Halo" means fluoro, chloro, bromo, or iodo, preferably fluoro and chloro.

[00035] "Haloalkyl" means alkyl substituted with one or more same or different halo atoms, e.g., -CH₂Cl, -CF₃, -CH₂CF₃, -CH₂CCl₃, and the like.

20 [00036] "Heteroaryl" means a monovalent monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. The heteroaryl ring is optionally substituted independently from each other with one or more substituents, preferably one or two substituents, selected from alkyl, haloalkyl, halo, nitro, cyano, amino, methylenedioxy, optionally substituted phenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, -V-OR', -VNR'R", V C(O)-R', V O-C(O)-R', -V- S(O)O-2-R'; -V-N-SO₂-R', -V-SO₂-NR'R", -V-N-C(O)-N-R'R", where V is absent or is a C1-C3 alkylene group and R' and R" are each independently from each other hydrogen,

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alkyl, haloalkyl, hydroxy, alkoxy, optionally substituted phenyl, cycloalkyl, heterocyclyl. More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thienyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidinyl, benzofuranyl, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, tetrahydroquinolyl, isoquinolyl, benzimidazolyl, benzisoxazolyl or benzothienyl, imidazo[1,2-a]-pyridinyl, imidazo[2,1-b]thiazolyl, and the derivatives thereof. "Heteroarylene" means a divalent monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment points of the heteroarylene radical will be on an aromatic ring. "Heteroarylene includes divalent versions of the heteroaryl radicals described above.

[00037] "Heteroarylalkyl" means a moiety of the formula -R'-R", where R' is alkylene and R" is heteroaryl as defined herein.

[00038] "Heterocyclyl" means a saturated or unsaturated non-aromatic cyclic radical of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or S(O)0-2, the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl group. The heterocyclyl ring may be optionally substituted independently from each other with one, two, or three substituents selected from alkyl, haloalkyl, halo, nitro, cyano, -V-optionally substituted phenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, -V-OR', VNR'R", -V-C(O)-R', -V-S(O)0-2-R'; -V-NR'-SO2-R", -V-SO2-NR'R", -V-N-C(O)-N-R'R", where V is absent or is a C1-C3 alkylene group and R' and R" are each independently from each other hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, optionally substituted phenyl, heteroaryl or cycloalkyl. More specifically the term heterocyclyl includes, but is not limited to, tetrahydropyranyl, piperidinyl, N-methylpiperidin-3-yl, piperazinyl, N-methylpyrrolidin-3-yl, 3-pyrrolidinyl, morpholinyl, thiomorpholinyl, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, pyrrolinyl, imidazolinyl, N-methanesulfonyl-piperidin-4-yl, and the derivatives thereof.

[00039] "Heterocycloalkyl" means a moiety of the formula -R'-R", where R' is alkylene and R" is heterocyclyl as defined herein.

[00040] "Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or a group capable of being displaced by a nucleophile and includes halo (such as chloro, bromo, and iodo), alkylsulfonyloxy, arylsulfonyloxy, alkylcarbonyloxy (e.g., acetoxy), arylcarbonyloxy, mesyloxy, tosyloxy, trifluoromethanesulfonyloxy, aryloxy (e.g., 2,4-dinitrophenoxy), methoxy, N,O-dimethylhydroxylamino, and the like.

[00041] "Optionally substituted phenyl" means a phenyl ring which is optionally substituted independently from each other with one or more substituents, preferably one or two substituents selected from the group consisting of alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, heteroalkyl, halo, nitro, cyano, amino, methylenedioxy, ethylenedioxy and acyl.

[00042] "Isomerism" means compounds that have identical molecular formulae but that differ in the nature or the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereoisomers", and stereoisomers that are non-superimposable mirror images are termed "enantiomers", or sometimes optical isomers. A carbon atom bonded to four nonidentical substituents is termed a "chiral center".

[00043] "Chiral isomer" means a compound with one chiral center. It has two enantiomeric forms of opposite chirality and may exist either as an individual enantiomer or as a mixture of enantiomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has $2^n - 1$ enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the Sequence Rule of Cahn, Ingold and Prelog. (Cahn et al, Angew. Chem. Inter. Edit. 1966, 5, 385; errata 511; Cahn et al., Angew. Chem. 1966, 78, 413; Cahn and Ingold, J. Chem. Soc. 1951 (London), 612; Cahn et al., Experientia 1956, 12, 81; Cahn, J., Chem. Educ. 1964, 41, 116).

[00044] "Geometric Isomers" means the diastereomers that owe their existence to hindered rotation about double bonds. These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[00045] "Atropic isomers" means the isomers owing their existence to restricted rotation caused by hindrance of rotation of large groups about a central bond.

[00046] The compounds of this invention may exist in stereoisomeric form, therefore they can be produced as individual stereoisomers or as mixtures.

[00047] "Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[00048] "Pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

[00049] (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

[00050] (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

5 [00051] It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same acid addition salt. "Crystal forms" (or polymorphs) means crystal structures in which a compound can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal
10 forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density hardness, crystal shape, optical and electrical properties, stability and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate.

[00052] "Solvates" means solvent addition forms that contain either stoichiometric or
15 non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water
20 retains its molecular state as H₂O, such combination being able to form one or more hydrate.

[00053] The terms "pro-drug" and "prodrug" are used interchangeably herein and refer to any compound which releases an active parent drug according to Formula I in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a
25 compound of Formula I are prepared by modifying one or more functional group(s) present in the compound of Formula I in such a way that the modification(s) may be cleaved in vivo to release the parent compound. Prodrugs include compounds of Formula I wherein a hydroxy, amino, sulfhydryl, carboxy or carbonyl group in a compound of Formula I is bonded to any group that may be cleaved in vivo to
30 regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, esters (e.g., acetate, dialkylaminoacetates, formates, phosphates, sulfates, and benzoate derivatives) and carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups, esters groups (e.g. ethyl esters, morpholinoethanol esters) of carboxyl functional groups, N-acyl derivatives

(e.g. N-acetyl) N-Mannich bases, Schiff bases and enaminones of amino functional groups, oximes, acetals, ketals and enol esters of ketone and aldehyde functional groups in compounds of Formula I, and the like, See Bundegaard, H. "Design of Prodrugs" p1-92, Elsevier, New York-Oxford (1985).

5 [00054] "Protecting group" (PG) refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T. W. Green and P. G. M. Futs, Protective Groups in Organic Chemistry, (Wiley, 3rd ed. 1999) and Harrison and Harrison et al., Compendium of Synthetic Organic Methods, Vols. 1-8 (John Wiley and Sons, 1971-
10 1996). Representative amino protecting groups include, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (Fmoc), nitro-veratryloxycarbonyl (NVOC), and the like. Representative hydroxy protecting
15 groups include those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

[00055] "Treating" or "treatment" of a disease includes: (1) preventing the disease, i.e., causing the clinical symptoms of the disease not to develop in a mammal that may be
20 exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; (2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or (3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

[00056] "A therapeutically effective amount" means the amount of a compound that,
25 when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[00057] "Prostaglandin analog" is a non-naturally-occurring compound which is
30 structurally similar to a prostaglandin.

[00058] "Prostaglandin receptor" or "prostanoid receptor" is a naturally-occurring protein that binds prostaglandins, which when bound alters the function of a cell. Prostaglandin receptors may be characterized as either excitatory or relaxant. Such

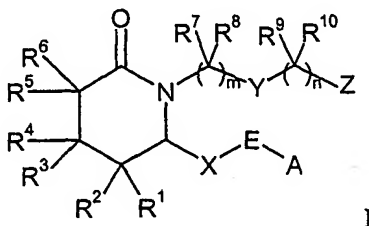
receptors include but are not limited to EP1, EP2, EP3, EP4, DP, FP, IP, TP1, and TP2. These receptors are further discussed by Coleman et al, in Pharmacological Reviews, 1994, Volume 6, No. 2, pages 205 - 229.

Nomenclature and Structures

- 5 [00059] In general, the nomenclature used in this Application is based on AUTONOMTM v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. Chemical structures shown herein are prepared using ISIS® v. 4.0. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen.

10 Compounds

[00060] The invention provides compounds of Formula I:



wherein:

m is from 1 to 4; preferably m is 2;

- 15 n is a bond or from 1 to 4; preferably n is 3;

A is alkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, cycloalkylalkyl, or aryloxyalkyl;

E is -CHOH- or -C(O)- (i.e., E is hydroxymethylene or oxo); preferably E is -CHOH- (hydroxymethylene);

X is -(CH₂)₂- or -CH=CH-;

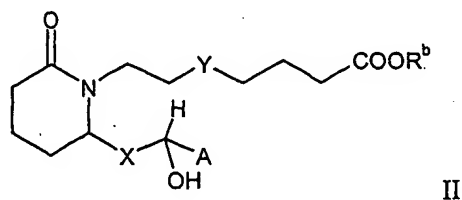
- 20 Y is -CH₂-, arylene, heteroarylene, -CH=CH-, -O-, -S(O)_p- where p is from 0 to 2, or -NR_a- where R_a is hydrogen or alkyl; preferably Y is -CH₂- or -S(O)_p-, with p preferably being 0;

Z is -CH₂OH, -CHO, tetrazol-5-yl, or -COOR_b where R_b is hydrogen or alkyl; preferably Z is -COOR_b and R_b is hydrogen;

R1, R2, R3, R4, R5, R6, R7, R8, R9 and R10 each independently are hydrogen or alkyl; preferably R1, R2, R3, R4, R5, R6, R7, R8, R9 and R10 are hydrogen; or a pharmaceutically acceptable salt or solvate, prodrug, single isomer or racemic or non-racemic mixture of isomers thereof.

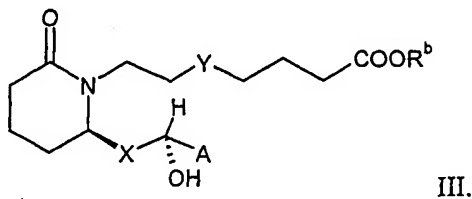
- 5 [00061] Where any of R1, R2, R3, R4, R5, R6, R7, R8, R9 R10, Ra and Rb are alkyl, they preferably are lower alkyl, i.e. C1-6alkyl, and more preferably C1-4alkyl.

[00062] In certain embodiments, m is 2, n is 3, E is -CHOH-, Y is -S- or -CH2-, Z is -COOR^b, and R1, R2, R3, R4, R5, R6, R7, R8, R9 and R10 are hydrogen. In such embodiments compounds of Formula I may be represented by Formula II:



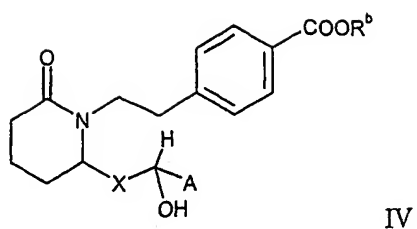
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wherein A, X, and R^b are as defined herein. In preferred embodiments, the stereochemistry may be such that compounds of Formula II are more specifically of Formula III:



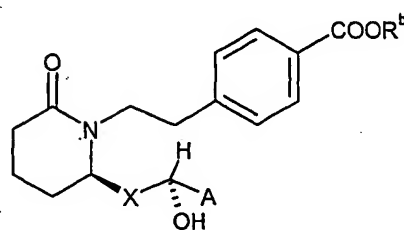
- 15 [00063] In other embodiments, m is 2, n is 0, E is -CHOH-, Y is arylene or phenylene, Z is -COOR^b, and R1, R2, R3, R4, R5, R6, R7, R8, R9 and R10 are hydrogen. In such embodiments compounds of Formula I may be represented by Formula IV:

- 14 -



IV

The stereochemistry may be such that compounds of Formula IV are more specifically of Formula V:

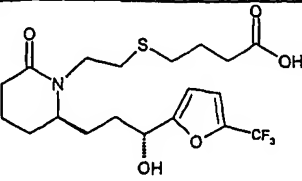
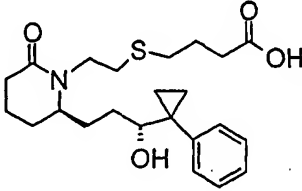
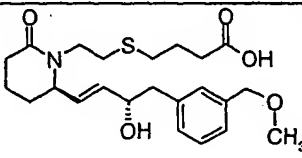
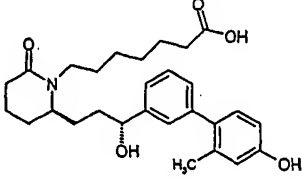
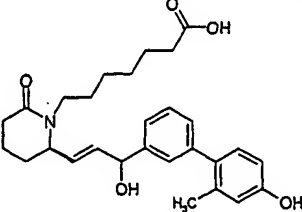
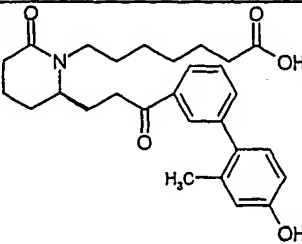


V.

5. [00064] Representative compounds in accordance with the invention are shown in Table 1.

TABLE 1

	Name (Autonom®)	Structure	Mass Spec (MW)
1	4-{2-[2 <i>R</i> -(5-cyclopropyl-3 <i>S</i> -hydroxy-pent-1 <i>E</i> -enyl)-6-oxo-piperidin-1-yl]ethylsulfanyl} butyric acid		369
2	4-(2-{2 <i>R</i> -[3 <i>R</i> -(4'-chloro-2'-methylbiphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl) butyric acid		503.5
3	7-{2 <i>R</i> -[3 <i>S</i> -hydroxy-4-(4-hydroxy-3-methyl-phenyl)-but-1 <i>E</i> -enyl]-6-oxo-piperidin-1-yl} heptanoic acid		403
4	7-{2 <i>R</i> -[3 <i>S</i> -hydroxy-4-(3-methoxymethyl-phenyl)-but-1 <i>E</i> -enyl]-6-oxo-piperidin-1-yl} heptanoic acid		417
5	7-{2 <i>R</i> -[3 <i>S</i> -hydroxy-4-(4-hydroxy-3-isopropyl-phenyl)-but-1 <i>E</i> -enyl]-6-oxo-piperidin-1-yl} heptanoic acid		431
6	4-(2-{2 <i>R</i> -[3-hydroxy-3-(1-phenylcyclopropyl)-prop-1 <i>E</i> -enyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid		417

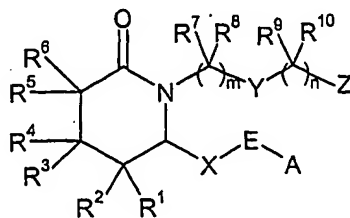
	Name (Autonom®)	Structure	Mass Spec (MW)
7	4-(2-{2 <i>R</i> -[3 <i>R</i> -3-hydroxy-3-(trifluoromethyl-furan-2-yl)-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl) butyric acid		437
8	4-(2-{2 <i>R</i> -[3 <i>R</i> -hydroxy-3-(1-phenylcyclopropyl)-propyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid		419
9	4-(2-{2 <i>R</i> -[3 <i>S</i> -hydroxy-4(3-methoxymethyl-phenyl)-but-1 <i>E</i> -enyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid		435
10	7-{2 <i>R</i> -[3 <i>R</i> -(4'-hydroxy-2'-methylbiphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl} heptanoic acid		467
11	7-{2 <i>R</i> -[3-hydroxy-3-(4'-hydroxy-2'-methylbiphenyl-3-yl)-prop-1 <i>E</i> -enyl]-6-oxo-piperidin-1-yl} heptanoic acid		465
12	7-(2-{2 <i>R</i> -[3 <i>R</i> -(4'-hydroxy-2'-methylbiphenyl-3-yl)-3-oxo-propyl]-6-oxo-piperidin-1-yl} heptanoic acid		465

	Name (Autonom®)	Structure	Mass Spec (MW)
13	4-{2-[2 <i>R</i> -(5-cyclobutyl-3 <i>S</i> -hydroxy-pent-1 <i>E</i> -enyl)-6-oxo-piperidin-1-yl]ethylsulfanyl} butyric acid		383
14	4-(2-{2 <i>R</i> -[3 <i>R</i> -(3'-fluorophenoxy-phenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl)-3-methyl butyric acid		503
15	4-{2-[2 <i>R</i> -(3-hydroxy-4,4-dimethyloct-1 <i>E</i> -enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl} butyric acid		399
16	7-{2 <i>R</i> -[3-hydroxy-3-(2,5-dimethylphenyl-3-yl)-prop-1 <i>E</i> -enyl]-6-oxo-piperidin-1-yl} heptanoic acid		387
17	7-[-2 <i>R</i> -(3-hydroxy-4-phenoxy-but-1 <i>E</i> -enyl)-6-oxo-piperidin-1-yl] heptanoic acid		389
18	7-{2 <i>R</i> -[3-hydroxy-3-(3'chloro-biphenyl-3-yl)-prop-1 <i>E</i> -enyl]-6-oxo-piperidin-1-yl} heptanoic acid		470.5

	Name (Autonom®)	Structure	Mass Spec (MW)
19	7-{2 <i>R</i> -[3 <i>R</i> -(3'-chloro-biphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl} heptanoic acid		472.5
20	4-(2-{2-[3-hydroxy-4-(3-trifluoromethyl-phenyl)-but-1 <i>E</i> -enyl]-6-oxo-piperidin-1-yl}-ethyl) benzoic acid		461
21	4-(2-{2-[3-hydroxy-3-(4'-chloro-2'-methyl-biphen-3-yl)-propyl]-6-oxo-piperidin-1-yl}-ethyl) benzoic acid		506.5

[00065] The compounds of the invention are capable of further forming pharmaceutically acceptable base addition salts. All of these forms are considered to be within the scope of the present invention.

5 [00066] In more detail, the invention relates to compounds of the Formula I



I

wherein:

m is from 1 to 4;

n is from 0 to 4;

A is alkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, cycloalkylalkyl, or aryloxyalkyl;

E is -CHOH- or -C(O)-;

X is $-(CH_2)_2-$ or $-CH=CH-$;

Y is $-CH_2-$, $-CH=CH-$, arylene, heteroarylene, $-O-$, $-S(O)_p-$ where p is from 0 to 2, or $-NRa-$ where Ra is hydrogen or alkyl;

Z is $-CH_2OH$, $-CHO$, tetrazole-5-yl or $-COORb$ where Rb is hydrogen or alkyl; and

5 R1, R2, R3, R4, R5, R6, R7, R8, R9 and R10 each independently are hydrogen or alkyl;

or a pharmaceutically acceptable salt, solvate, prodrug, single isomer or racemic or non-racemic mixture of isomers thereof.

[00067] More preferably, in the above compounds E is $-CHOH-$. Another preferred

10 embodiment of the present invention comprises compounds wherein Z is $-COORb$.

In the above compounds Y is $-CH_2-$ or in further preferred compounds Y is

$S(O)_p-$ and p is 0 or Y is arylene. In further preferred compounds X is $-CH=CH-$ or

X is $-(CH_2)_2-$. In a further preferred embodiment of the present invention in the

above compounds A is independently selected from the group consisting of alkyl,

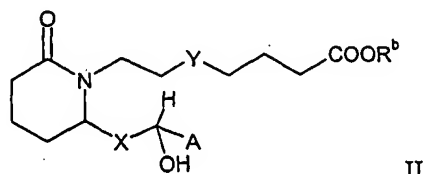
15 aryl, heteroaryl, arylalkyl, arylcycloalkyl, cycloalkylalkyl and aryloxyalkyl. More

preferably A is alkyl or A is aryl or A is heteroaryl or A is arylalkyl or A is

arylalkyl or A is cycloalkylalkyl or A is aryloxyalkyl.

[00068] Preferred compounds of the present inventions are compounds of the Formula

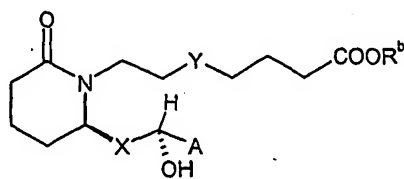
II



II

20

wherein Y is $-CH_2-$ or $-S-$, and A, X and Rb are as defined any above. Further preferred compounds are compounds of the Formula III:



III

wherein A, X, Y and Rb are as defined above. In these compounds X is preferably -CH=CH- and Y is preferably arylene. Preferred compounds may be selected from the group comprising:

- a. 4-{2-[(R)-2-((S)-(E)-5-Cyclopropyl-3-hydroxy-pent-1-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl}-butyric acid;
- b. 4-(2-{2R-[3R-(4'Chloro-2'methylbiphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl) butyric acid;
- c. 7-{2R-[3S-Hydroxy-4-(4-hydroxy-3-methyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic;
- d. 7-{2R-[3S-Hydroxy-4-(3-methoxymethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid;
- e. 7-{2R-[3S-Hydroxy-4-(4-hydroxy-3-isopropyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid;
- f. 4-(2-{2R-[3-Hydroxy-3-(1-phenylcyclopropyl)-prop-1E-enyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid;
- g. 4-(2-{2R-[3R-3-Hydroxy-3-(trifluoromethyl-furan-2-yl)-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl) butyric;
- h. 4-(2-{2R-[3R-Hydroxy-3-(1-phenylcyclopropyl)-propyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid ;
- i. 4-(2-{2R-[3S-Hydroxy-4-(3-methoxymethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid;
- j. 7-{2R-[3R-(4'-Hydroxy-2'-methylbiphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl} heptanoic acid;
- k. 7-{2R-[3-Hydroxy-3-(4'-hydroxy-2'methylbiphenyl-3-yl)-prop-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid;
- l. 7-(2-{2R-[3R-(4'-Hydroxy-2'methylbiphenyl-3-yl)-3-oxo-propyl]-6-oxo-piperidin-1-yl} heptanoic acid;
- m. 4-{2-[2R-(5-Cyclobutyl-3S-hydroxy-pent-1E-enyl)-6-oxo-piperidin-1-yl]ethylsulfanyl} butyric acid;
- n. 4-(2-{2R-[3R-(3'-fluorophenoxy-phenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl) 3-methyl-butyric acid;
- o. 4-{2-[2R-(3-Hydroxy-4,4-dimethyl-oct-1E-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl} butyric acid;
- p. 7-{2R-[3-Hydroxy-3-(2,5-dimethylphenyl-3-yl)-prop-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid;
- q. 7-[2R-(3-Hydroxy-4-phenoxy-but-1E-enyl)-6-oxo-piperidin-1-yl] heptanoic acid;

- r. 7-{2R-[3-Hydroxy-3-(3'chloro-biphenyl-3-yl)-prop-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid;
- s. 7-{2R-[3R-(3'chloro-biphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl} heptanoic acid;
- 5 t. 4-(2-{2-[3-Hydroxy-4-(3-trifluoromethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl}-ethyl) benzoic acid;
- u. 4-(2-{2-[3-Hydroxy-4-(3-trifluoromethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl}-ethyl) benzoic acid; and
- v. 3, 4-(2-{2-[3-(4'chloro-2'-methyl-biphen-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl}-ethyl) benzoic acid.
- 10

[00069] The invention also comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined above in admixture with at least one suitable carrier diluent or excipient. Further the invention comprises a method of treatment of a disease in a mammal treatable by administration of a selective EP4 prostaglandin agonist comprising administration to the mammal a therapeutically effective amount of a compound as defined above. The disease may be associated with bone disorders, e.g. osteoporosis. The compounds of the present invention may be used in therapy, e.g. for the manufacture of medicaments, e.g. for the treatment of bone disease, e.g. osteoporosis. The invention also refers to a process for the production of compounds as described above comprising the steps described in schemes 1 to 3.

15

20

Synthesis

25 [00070] Compounds of the invention can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below.

[00071] The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis; Wiley & Sons: New York, 1991, Volumes 1-15; Rodd's Chemistry of Carbon Compounds, Elsevier Science Publishers, 1989, Volumes 1-5 and

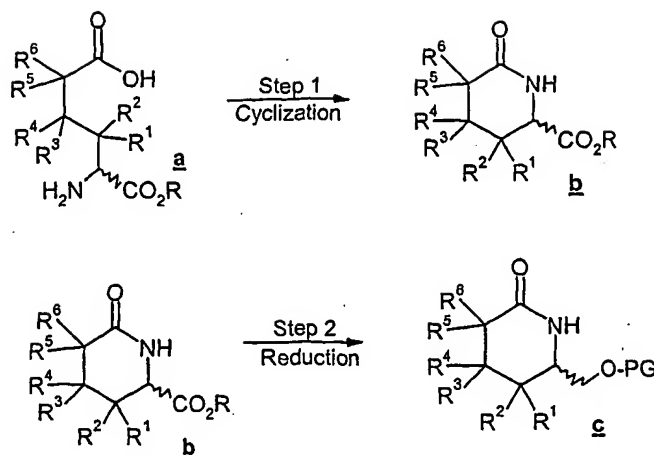
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Supplementals; and Organic Reactions, Wiley & Sons: New York, 1991, Volumes 1-40. The following synthetic reaction schemes are merely illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this Application.

[00072] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

[00073] Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about -78 C to about 150 C, more preferably from about 0 C to about 125 C, and most preferably and conveniently at about room (or ambient) temperature, e.g., about 20 C.

[00074] Schemes A, B, and C below illustrate synthetic procedures usable to prepare compounds of Formula I, wherein LG is a leaving group, PG is a protecting group, R is any lower alkyl and may be the same or different in each occurrence, and m, n, A, X, Y, Z, R1, R2, R4, R6, R7, R8, R9 and R10 are as defined herein. Specific examples of the procedure of Scheme A are provided in the following Experimental section.

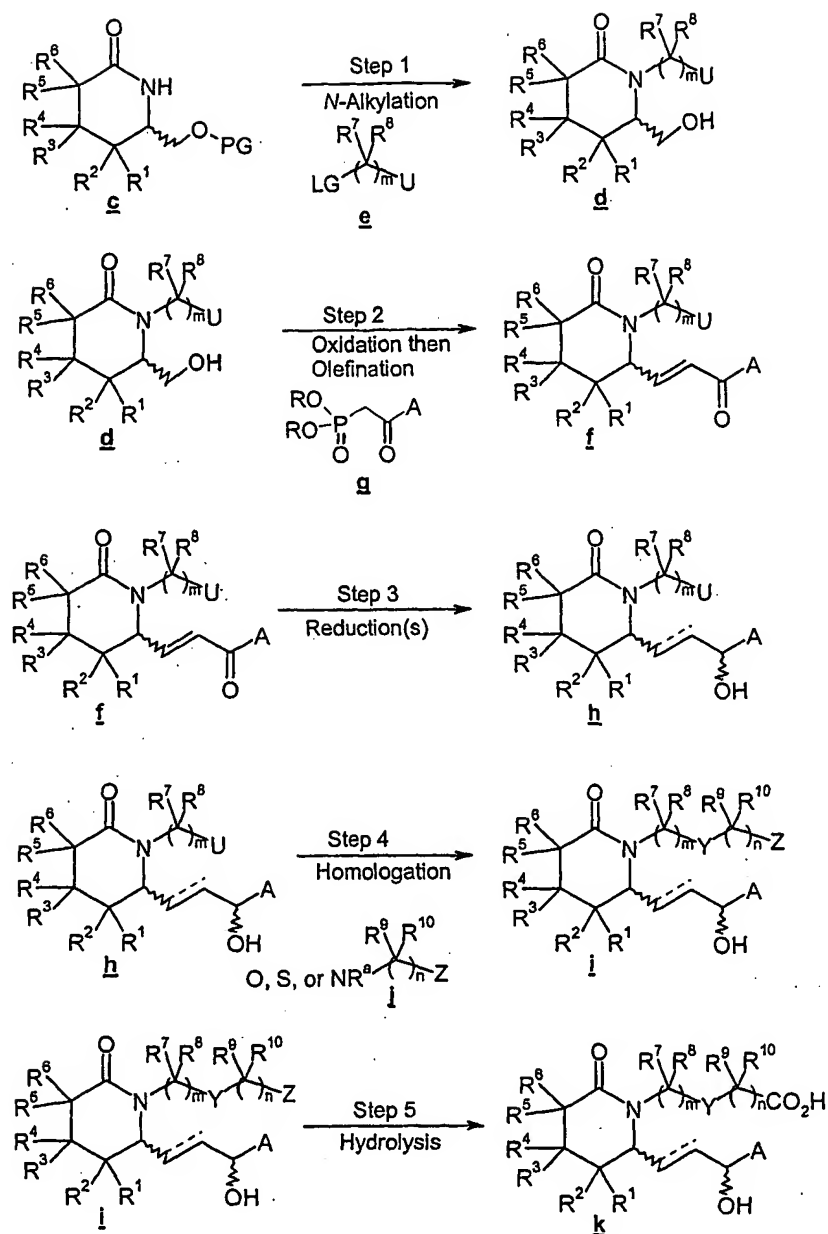


SCHEME A

[00075] Scheme A illustrates the preparation of In step 1 of Scheme A, an amino adipic acid **a** is cyclized to form a delta-lactam **b**. Various amino adipic acids of R and S configuration usable in step 1 are commercially available or may be prepared via well known techniques. The cyclization of this step may be carried out, for example, by simple heating of the amino adipic acid in acetic acid or other polar protic solvent conditions preferably under acidic conditions.

[00076] Reduction of a carboxylate group of delta lactam **b** is carried out in step 2, followed by protection of the reduction product to yield a protected alcohol **c**. The reduction of step 2 may be achieved by, for example, treatment of delta lactam **b** with an alkali metal borohydride or cyanoborohydride under mild, polar protic conditions. The resulting alcohol (not shown) may then be protected, for example, by treatment with alkyl vinyl ether in the presence of trifluoroacetic acid to protect the alcohol as an acetal. The protection of hydroxyl groups via acetal formation is described by S. Saijo et al. Chem. Pharm. Bull.1980, 28, 1449-1458. Protection of the hydroxyl of compound **c** may also be achieved via silylation as described in T. W. Green and P. G. M. Futs, Protective Groups in Organic Chemistry, (Wiley, 3rd ed. 1999).

[00077] Scheme B below illustrates the preparation of compounds of Formula I. The procedure of Scheme B may be used in embodiments wherein Y is O, S or NRa or wherein Y can otherwise act as a nucleophile.



SCHEME B

[00078] In step 1 of Scheme B, an N-alkylation of the lactam nitrogen of the protected alcohol c from Scheme A occurs. This alkylation may be effected by treatment of the protected alcohol c with a base such as sodium hydride or potassium hexamethyldisilazide at reduced temperature under inert atmosphere, followed by

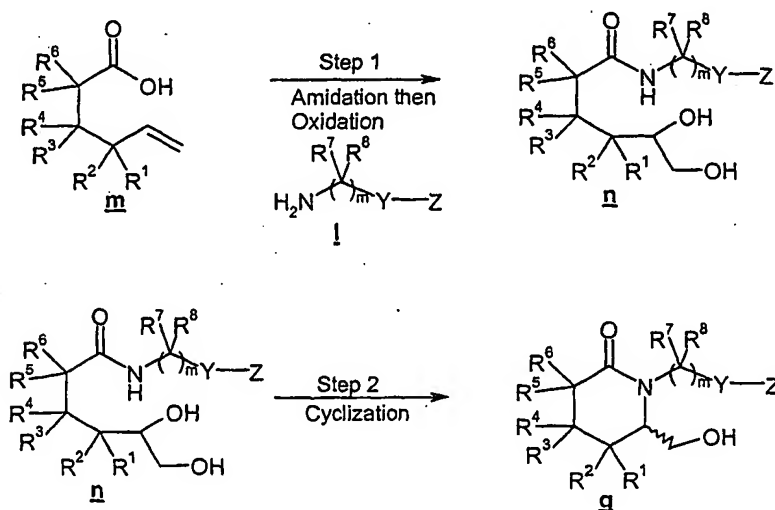
reaction with alkylating agent e. The resulting alkylated product (not shown) is then deprotected by treatment with acid to provide alcohol d. The leaving group LG may comprise a halo, tosyl or other suitable leaving group. The group U in Scheme B may be a protected alcohol (-O-PG) or may be R⁹R¹⁰CnZ.

- 5 [00079] In step 2, the alcohol e of step 1 is oxidized to an aldehyde (not shown) by mild oxidation with the combination of dimethylsulfoxide and oxalyl chloride, Dess-Martin periodinane, the combination of TEMPO and sodium hypochlorite, PCC, PDC or the like. The aldehyde is immediately reacted with a phosphonic acid dialkyl ester compound g in the presence of base under polar aprotic conditions to
- 10 give an enone condensation product f.
- [00080] In step 3, the condensation product f of step 5 may optionally undergo reduction of the carbonyl and/or unsaturation present in the compound f, to provide a compound h. Stereoselective reduction of the carbonyl group of compound f using the "CBS" reagents as described by E. J. Corey, et al., J. Am. Chem. Soc. 1987, 109,
- 15 7925-7926 or other stereoselective reducing agent may be utilized in this step. If the preferential formation of one of the diastereomers is desired such as the S-hydroxyl isomer of Formula I when A is alkyl, arylalkyl, cycloalkylalkyl, or aryloxyalkyl, the stoichiometric combination of lithium aluminum hydride-ethanol-(S)-(-)-binaphthol as described by R. Noyori, et al., J. Am. Chem. Soc. 1984, 106, 6717-6725
- 20 can be used; or if the R-hydroxyl isomer is desired, the combination of catalytic amounts of (R)-2-methyl-"CBS"-oxazaborolidine with stoichiometric borane-dimethyl sulfide as described by E. J. Corey, et al., J. Am. Chem. Soc. 1987, 109, 7925-7926; or stoichiometric amounts of (R)-3-pinanyl-9-borabicyclo[3.3.1]nonane as described by M. M. Midland et al., J. Am. Chem. Soc. 1980, 102, 867-869 is used. 1,2
- 25 Reduction may be effected with a hydride such as sodium borohydride, for example, in a solvent such as dichloromethane, toluene, ethanol, or tetrahydrofuran. The combination of a lanthanide salt such as cerium (III) chloride with sodium borohydride may also be used when A is aryl or heteroaryl. Catalytic hydrogenation of the double bond with Raney Ni or Pd on carbon yields a saturated side chain.
- 30 [00081] In step 4, homologation of compound h occurs wherein the group U is displaced by reaction with nucleophilic compound j to yield compound i. Where Z is a carboxylate, hydrolysis to the corresponding acid k may optionally be carried out by procedures well known by the artisan, such as addition of a base such as lithium, sodium or potassium hydroxide, or an acid such as sulfuric acid or hydrochloric acid

in a protic or ethereal solvent containing water, or by employing a Lipase type VII in 0.05 M aqueous phosphate buffer at pH 6.8 as described by C. Luthy, et al. J. Am. Chem. Soc. 1978, 100, 6211-6217.

[00082] Many variations on the procedure of Scheme B may be used. For example, in certain embodiments the delta lactam c may be N-alkylated in step 1, and the N-alkylated lactam may then subsequently be converted to an aldehyde and then alkylated and selectively reduced to provide a compound of Formula I. In another variation, enone f may be reacted with a metal or a magnesium halide of general formula R11M where R11 is alkyl, to introduce an additional group to the carbon attached to group A. Other variations on Scheme B are possible and will suggest themselves to those skilled in the art. Where necessary, conventional protecting group schemes may be used in association with groups A, Y and Z.

[00083] Another synthetic route to the subject compounds is shown in Scheme C below, that is preferred for embodiments wherein n is 0, Y is aryl or heteroaryl, and A, X, Z, R1, R2, R4, R6, R7, R8, R9 and R10 are as defined herein.



SCHEME C

[00084] In step 1 of Scheme C, a 5-hexenoic acid m is reacted with an amine l and then subject to dihydroxylation of its double bond, to form amide n. 5-Hexenoic acids usable in step 1 are commercially available or can be prepared by well-known techniques.

[00085] The amide compound n is cyclized in step 2 to provide a delta lactam alcohol q.

This cyclization process may be effected following protection of the primary hydroxyl of compound n. A suitable protecting agent such as t-butyl-dimethylsilyl trifluoromethanesulfonate or benzyl 2,2,2-trichloroacetimidate will, respectively, furnish the silyl or benzyl ether protecting groups. The secondary hydroxyl of n may then be activated for displacement by treatment with alkyl or aryl sulfonyl chloride such as methanesulfonyl chloride. The amide-secondary sulfonate (not shown) may then be treated with a base such as an alkali metal hydride or alkoxide in a polar medium such as methanol, tetrahydrofuran, or N,N-dimethylformamide to effect the cyclization. The pendent primary ether may be deprotected by the action of fluoride (tetrabutylammonium fluoride) in the case a silyl ether or catalytic hydrogenolysis (Pd-C under hydrogen gas) in the case of a benzyl ether. Compound q may then be processed according to Scheme B, Steps 2-5, to afford compounds of Formula I. If the R-enantiomer of q were desired, asymmetric dihydroxylation, according to M. Shipman, et al. Synthesis 1998, 1141-1144, may be used.

Administration and Pharmaceutical Composition

[00086] The present invention includes pharmaceutical compositions comprising at least one compound of the present invention, or an individual isomer, racemic or non-racemic mixture of isomers or a pharmaceutically acceptable salt or solvate thereof, together with at least one pharmaceutically acceptable carrier, and optionally other therapeutic and/or prophylactic ingredients.

[00087] In general, the compounds of the present invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Suitable dosage ranges are typically 0.001-50 mg daily, preferably 0.005-10 mg daily, and most preferably 0.010-1.0 mg daily, depending upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this Application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease.

[00088] In general, compounds of the present invention will be administered as pharmaceutical formulations including those suitable for oral (including buccal and sub-lingual), rectal, nasal, topical, pulmonary, vaginal, or parenteral (including intramuscular, intraarterial, intrathecal, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The preferred manner of administration is generally oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

[00089] A compound or compounds of the present invention, together with one or more conventional adjuvants, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. Formulations containing about one (1) milligram of active ingredient or, more broadly, about 0.01 to about one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

[00090] The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms. The pharmaceutical compositions and dosage forms may comprise a compound or compounds of the present invention or pharmaceutically acceptable salts thereof as the active component. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about

- one (1) to about seventy (70) percent of the active compound. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term
- 5 "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier, providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges may be as solid forms suitable for oral administration.
- 10 [00091] Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents, for example,
- 15 such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose,
- 20 and other well known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.
- [00092] The compounds of the present invention may be formulated for parenteral
- 25 administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of
- 30 oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid

or by lyophilization from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

[00093] The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatine and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[00094] The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

[00095] The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[00096] The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example, with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

[00097] The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of five (5) microns or less. Such a particle size

may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g., gelatine or blister packs from which the powder may be administered by means of an inhaler.

[00098] When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient. For example, the compounds of the present invention can be formulated in transdermal or subcutaneous drug delivery devices. These delivery systems are advantageous when sustained release of the compound is necessary and when patient compliance with a treatment regimen is crucial. Compounds in transdermal delivery systems are frequently attached to an skin-adhesive solid support. The compound of interest can also be combined with a penetration enhancer, e.g., Azone (1-dodecylazacycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into the subdermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, e.g., silicone rubber, or a biodegradable polymer, e.g., polylactic acid.

[00099] The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

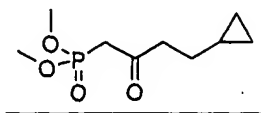
[000100] Other suitable pharmaceutical carriers and their formulations are described in 1 invention are described in Examples 4.

EXAMPLES

[000101] The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Preparation 1

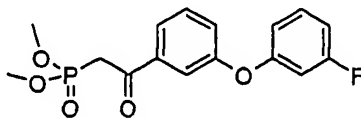
(4-Cyclopropyl-2-oxo-butyl)phosphonic acid dimethyl ester



[000102] A suspension of sodium hydride (Aldrich, 95%, 760 mg, 31.6 mmol) in anhydrous tetrahydrofuran (90 mL) at ambient temperature was treated with dimethyl (2-oxo-propyl) phosphonate (Sigma, 5.0 g, 30.6 mmol) in tetrahydrofuran (10 mL) over 40 minutes and then cooled to 0 °C. The suspension was treated with normal butyllithium (2.5 M in hexanes, 13.2 mL, 33 mmol) and the resulting solution was stirred at 0 °C for 2 hours. Bromocyclopropane (3.1 mL, 32 mmol) was added in tetrahydrofuran (10 mL) and the mixture was stirred at 0 °C for 1.5 hours and ambient temperature for 1 hour and then treated with ethanol (2 mL). The mixture was partitioned between 0.3 M aqueous HCl (150 mL) and dichloromethane (2 x 100 mL). The combined organic extracts were washed with brine and stored over anhydrous sodium sulfate. (4-Cyclopropyl-2-oxo-butyl)phosphonic acid dimethyl ester (2.11 g) was obtained after silica gel chromatography, eluted with 2:1 ethyl acetate:hexane as an oil: ¹H NMR (300 MHz, CDCl₃) 3.74 (d, J = 11.4 Hz, 6 H), 3.06 (d, J = 22.8 Hz, 2 H), 2.67 (t, J = 7.2 Hz, 2 H), 1.43 (q, J = 7.2 Hz, 2 H), 0.61-0.72 (m, 1 H), 0.35-0.42 (m, 2 H), -0.03-0.08 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) 202.0 (d, J = 6.0 Hz), 53.1 (d, J = 6.3 Hz), 44.2, 41.4 (d, J = 128 Hz), 28.6, 10.3, 4.5.

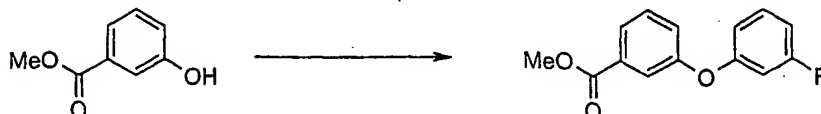
Preparation 2

[2-[3-(3-Fluorophenoxy)-phenyl]-2-oxo-ethyl]phosphonic acid dimethyl ester



Step 1:

3-(3-Fluorophenoxy) benzoic acid methyl ester

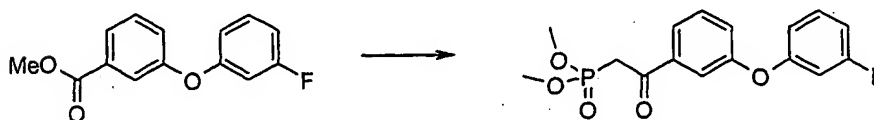


[000103]

A suspension of methyl 3-hydroxybenzoic acid (5.4 g, 35.5 mmol), 3-fluorophenylboronic acid (5.5 g, 35.5 mmol), cupric acetate (7.1 g, 35.5 mmol), 3 Å molecular sieves (9 g), pyridine (12 mL, 145 mmol) in dichloromethane (220 mL) was stirred at ambient temperature under ambient atmosphere. After 11 days, the mixture was filtered through Celite® and the volatiles were removed from the filtrate. The 3-(3-fluorophenoxy) benzoic acid methyl ester (3.68 g) was eluted from silica gel column with 5:1 hexane:ethyl acetate and taken onto the next step.

Step 2

{2-[3-(3-Fluorophenoxy)-phenyl]-2-oxo-ethyl}phosphonic acid dimethyl ester



15

[000104] A tetrahydrofuran (100 mL) solution of dimethyl methylphosphonate (4.0 mL, 37.5 mmol) was cooled to -78 °C under argon and treated with normal butyllithium (15.0 mL, 2.5 M hexane solution, 37.5 mmol) and allowed to stir for 45 minutes. The ester obtained from step 1 (4.62 g, 18.7 mmol) was dissolved in tetrahydrofuran (15 mL) and added to the solution above at -78 °C and the resulting mixture was stirred at 0 °C for 1 hour. At which time, the yellow solution was partitioned between aqueous ammonium chloride (100 mL) and ethyl ether (200 mL). The organic portion was washed with fresh water (3 x 30 mL), then brine, and stored over anhydrous sodium sulfate. Following filtration and removal of the volatiles in vacuo, the desired -ketophosphonate (5.8 g) was obtained as a viscous oil: ¹H NMR (300 MHz, CDCl₃) 7.78 (dt, J = 0.6, 0.9, 7.8 Hz, 1 H), 7.63 (t, J = 2.1 Hz, 1 H), 7.48 (t, J =

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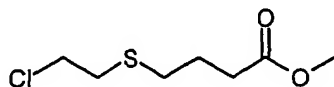
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8.1 Hz, 1 H), 7.32-7.26 (m, 2 H), 6.90-6.78 (m, 2 H), 6.70 (dt, J = 2.4, 9.9 Hz, 1 H), 3.80 (d, J = 11.2 Hz, 6 H), 3.61 (d, J = 22.6 Hz, 2 H).

Preparation 3

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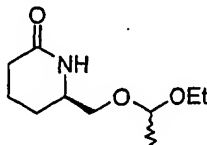
Methyl 4-[(2-chloroethyl)thio]butanoate



[000105] A 0 °C isopropanol (70 mL) solution of 4-mercaptobutyric acid (3.85 g, 20 mmol) was treated with sodium hydride in four portions (95%, 1.56 g total, 65 mmol) over 20 minutes and allowed to warm to room temperature. 1-Bromo-2-chloroethane (11 mL, 128 mmol) was added rapidly with the resulting suspension stirred vigorously for 2 days, then the volatiles were removed, and the residue was partitioned between 5% aqueous acetic acid and ethyl acetate. The combined organic extracts were washed with brine and stored over sodium sulfate. The extract was filtered and the volatiles were removed under vacuum. The residue was dissolved in methanol (60 mL) and cooled to 0 °C under argon atmosphere. Thionyl chloride (5 mL, 69 mmol) was added dropwise and the solution was stirred at room temperature. After 2-3 hours, the volatiles were removed, toluene was added, and the volatiles were removed again. Chromatography yielded (2.93 g, 14 mmol) of methyl 4-[(2-chloroethyl)thio]butanoate as a colorless oil: MS (NH₃) m/z 199 (M+1⁺ with ³⁷Cl), 197 (M⁺+ with ³⁵Cl).

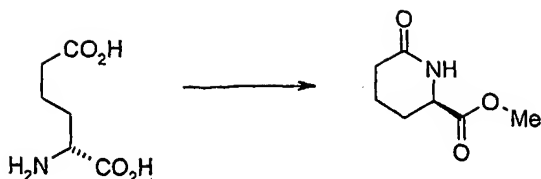
EXAMPLE 1

6R-(1-Ethoxy-ethoxymethyl)-piperidin-2-one



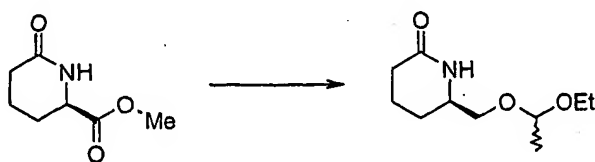
Step 1: 6-Oxo-piperidine-2R-carboxylic acid methyl ester

- 35 -



[000106] An acetic acid (30 mL) solution of R-2-aminoadipic acid (5 g, 31 mmol, Sigma Chemical Co.) was heated to reflux for six hours. Upon cooling, the volatiles were removed with a rotary evaporator and then the aid of a toluene azeotrope (2 x 25 mL). The residue was dissolved in methanol (15 mL) and dichloromethane (30 mL) at ambient temperature. The solution was treated with a (trimethylsilyl)diazomethane (30 mL, 2 M in hexanes, Aldrich) and the golden solution was stirred for 4 hours. The solution was treated with drops of acetic acid until the golden color dissipated and the volatiles were removed with a rotary evaporator. The residue was loaded onto a pad of silica gel and washed with 1:1 dichloromethane and ethyl acetate. 6-Oxo-piperidine-2R-carboxylic acid methyl ester, eluted with ethyl acetate, was obtained as a tan oil (4.3 g): [α]_D +12.0 (c.1.0, CHCl₃) and the ¹H NMR matched the literature report (C. E. Davies et al. Synthetic Commun. 1996, 26, 687-696).

Step 2: 6R-(1-Ethoxy-ethoxymethyl)-piperidin-2-one

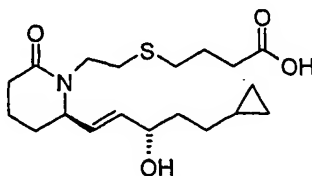


[000107] An ethanol (400 mL) solution of 6-oxo-piperidine-2R-carboxylic acid methyl ester (13.7 g, 87 mmol) was moderated with a tap-water bath under an Argon atmosphere and treated with sodium borohydride in three equal portions over 15 minutes (4.2 g, 109 mmol total). The reaction mixture was stirred for three hours at ambient temperature and then treated with acetic acid until an aliquot was about pH 4. The volatiles were removed with a rotary evaporator and the residue was loaded onto a pad of silica gel. 6R-Hydroxymethyl-piperidin-2-one was eluted with 5% methanol in dichloromethane and obtained as an oil. The oil (6.3 g, 49 mmol) was used directly by treatment with ethyl vinyl ether (7.0 mL, 73 mmol) and trifluoroacetic acid (1 mL) in dichloromethane (200 mL) at ambient temperature. After two hours, the solution was treated with aqueous sodium bicarbonate, extracted

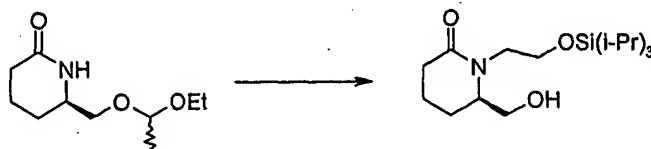
with dichloromethane (2 x 50 mL), and stored over anhydrous sodium sulfate. The 6R-(1-ethoxy-ethoxymethyl)-piperidin-2-one was obtained as an oil (6.9 g, 29 mmol) after filtration and removal of the volatiles: ¹H NMR (300 MHz, CDCl₃) 6.14-6.24 (br.s, 1 H), 4.67-4.76 (m, 1 H), 3.18-3.67 (m, 5 H), 2.23-2.47 (m, 3 H), 1.64-1.98 (m, 3 H), 1.31 (dd, 3 H), 1.20 (dt, 3 H).

EXAMPLE 2

4-{2-[(R)-2-((S)-(E)-5-Cyclopropyl-3-hydroxy-pent-1-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl}-butyric acid



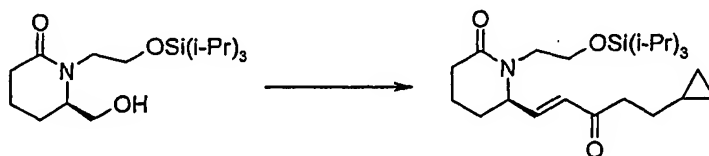
Step 1: 6R-Hydroxymethyl-1-(2-triisopropylsilanyloxy-ethyl)-piperidin-2-one



[000108] A dimethylformamide (70 mL) solution of 6R-(1-ethoxy-ethoxymethyl)-piperidin-2-one from Example 1 (6.9 g, 34 mmol) and potassium iodide (5.7 g, 34 mmol) was cooled to 0° C under an Argon atmosphere. Sodium hydride (95%, 910 mg, 36 mmol) was added in one portion, and the bubbling mixture was allowed to warm to ambient temperature. After 1.5 hours, the mixture was treated with 2-bromoethanol tri-isopropylsilyl ether (10.5 g, 37.2 mmol) in dimethylformamide (15 mL) and warmed to 50° C for 40 hours. The volatiles were removed by short-path distillation (5 mmHg, pot temperature to 75° C) and the resulting pot residue was partitioned between water (100 mL) and 1:1 hexane:ethyl acetate (4 x 100 mL). The combined organic extracts was washed with water (2 x 25 mL) then brine and stored over anhydrous sodium sulfate. The solution was filtered and the volatiles were removed with a rotary evaporator.

[000109] The resulting tan oil (15.3 g) was directly treated with ethanol (150 mL) and pyridinium p-toluene sulfonic acid (800 mg, 3.2 mmol) and heated to reflux. After 60 minutes, the solution was cooled and treated with 5% aqueous sodium bicarbonate (20 mL) and the volatiles were removed with a rotary evaporator. The residue was loaded onto a pad of silica gel and washed with 2:1 ethyl acetate:hexane. 6R-Hydroxymethyl-1-(2-triisopropylsilyloxy-ethyl)-piperidin-2-one (5.22 g, 15.8 mmol) was eluted with ethyl acetate: [$[\text{D}]_{\text{D}}^{-37.5}$ (c.1.0, CH_3CN); IR (cm^{-1}) 3373, 2943, 2865, 1617, 1465; ^1H NMR (300 MHz, CDCl_3) 4.11-4.20 (m, 1 H), 3.61-3.90 (m, 5 H), 3.42-3.53 (m, 2 H), 2.36-2.41 (m, 2 H), 1.63-1.99 (m, 4 H), 1.07 (s, 21 H); ^{13}C NMR (75 MHz, CDCl_3) 172.1, 64.8, 62.7, 61.0, 50.1, 32.8, 26.4, 18.7, 18.3, 12.2; MS (ES) m/z 330 (M^{+1}) $^+$.

Step 2: 6R-(5-Cyclopropyl-3-oxo-pent-1E-enyl)-1-(2-triisopropylsilyloxy-ethyl)-piperidin-2-one

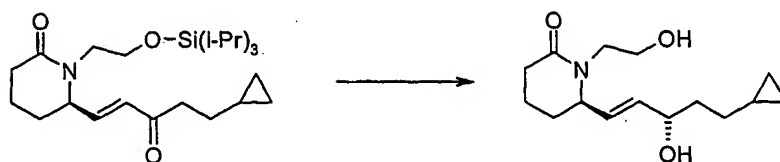


[000110] A -78°C dichloromethane solution of anhydrous dimethyl sulfoxide (0.87 mL, 11.2 mmol) under an Argon atmosphere was treated with oxalyl chloride (2 M CH_2Cl_2 solution, 3.9 mL, 7.8 mmol), which was added over a 3 minute period. After 20 minutes, a dichloromethane (10 mL) solution of 6R-hydroxymethyl-1-(2-triisopropylsilyloxy-ethyl)-piperidin-2-one from step 1 (1.85 g, 5.6 mmol) was added dropwise. The resulting yellow solution was stirred for 15 minutes at -78°C and then treated rapidly with triethylamine (2.3 mL, 16.8 mmol), after which the cooling bath was removed. After 30 minutes, the suspension was poured into aqueous sodium bicarbonate and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were stored over anhydrous sodium sulfate. The extract was filtered and the volatiles were removed to yield the aldehyde as a tan oil (1.75 g), which was used directly.

[000111] The crude aldehyde (875 mg, 2.65 mmol) was dissolved in acetonitrile (25 mL) and treated with (4-cyclopropyl-2-oxo-butyl) phosphonic acid dimethyl ester (670 mg, 3.05 mmol), lithium chloride (135 mg, 3.2 mmol), and diisopropylethylamine (0.51 mL, 2.9 mmol). After stirring the suspension at ambient temperature for 2.5

hours, it was poured into ether and aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (4 x 30 mL) and stored over anhydrous sodium sulfate. The extract was filtered, volatiles removed in vacuo, and the residue subjected to silica gel chromatography. 6R-(5-Cyclopropyl-3-oxo-pent-1E-enyl)-1-(2-triisopropylsilyloxy-ethyl)-piperidin-2-one (793 mg, 1.85 mmol) was obtained as an oil: ¹H NMR (300 MHz, CDCl₃) 6.70 (dd, J = 5.5, 15.8 Hz, 1 H), 6.11 (dd, J = 0.6, 15.8 Hz, 1 H), 4.52-4.59 (m, 1 H), 4.06-4.14 (m, 1 H), 3.95 (dt, J = 3.6, 9.3 Hz, 1 H), 3.71-3.80 (m, 1 H), 2.70-2.79 (m, 1 H), 2.66 (t, J = 6.9 Hz, 1 H), 2.37-2.44 (m, 1 H), 1.96-2.05 (m, 1 H), 1.49-1.88 (m, 6 H), 1.05 (s, 22 H), 0.64-0.73 (m, 1 H), 0.39-0.44 (m, 2 H), 0.02-0.07 (m, 2 H).

Step 3: 6R-(5-Cyclopropyl-3S-hydroxy-pent-1E-enyl)-1-(2-hydroxyethyl)-piperidin-2-one



[000112] A 0 °C toluene (10 mL) solution of (R)-2-methyl-CBS-oxazaborolidine (0.20 mL, 1.3 mmol, 5 M ethyl ether solution) under an argon atmosphere was generated. 6R-(5-Cyclopropyl-3-oxo-pent-1E-enyl)-1-(2-triisopropylsilyloxy-ethyl)-piperidin-2-one (793 mg, 1.85 mmol) was added in anhydrous toluene (5 mL) dropwise and stirred at 0° for 20 minutes. The solution was quenched with HCl (1.5 mL, 2 M solution in methanol) and the volatiles were removed in vacuo to yield a solid residue. The residue was redissolved in methanol and the volatiles were removed again in vacuo. The residue was loaded onto a column of silica gel and 6R-(5-cyclopropyl-3S-hydroxy-pent-1E-enyl)-1-(2-triisopropylsilyloxy-ethyl)-piperidin-2-one (541 mg) was eluted with a gradient of 2 - 6% iso-propanol in 3:1 hexane:ethyl acetate and used directly.

[000113] 6R-(5-Cyclopropyl-3S-hydroxy-pent-1E-enyl)-1-(2-triisopropylsilyloxy-ethyl)-piperidin-2-one (541 mg, 1.26 mmol) was dissolved in THF (10 mL) and treated with tetrabutylammonium fluoride hydrate (480 mg, 1.5 mmol). The solution was stirred for 2.5 h at room temperature, diluted with 10 mL hexane and loaded onto a pad of silica gel. 6R-(5-Cyclopropyl-3S-hydroxy-pent-1E-enyl)-1-(2-

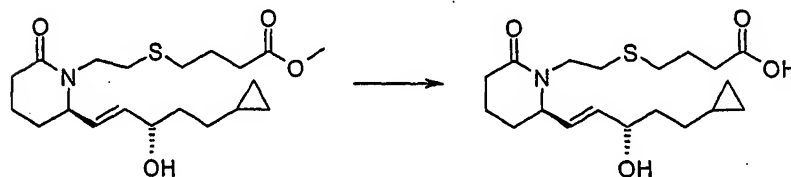
hydroxyethyl)-piperidin-2-one (328 mg, 1.23 mmol) eluted with 10% ethanol in ethyl acetate and obtained as an oil, ¹H NMR (300 MHz, CDCl₃-D₂O, partial spectrum) 5.64-5.59 (m, 2 H), 4.22-4.18 (m, 1 H), 4.03-3.98 (m, 1 H), 3.80-3.69 (m, 3 H), 3.31-3.20 (m, 1 H), 0.72-0.61 (m, 1 H), 0.48-0.40 (m, 2 H), 0.08-0.00 (m, 2 H); MS: *m/z* 268 (M⁺)⁺, 250 (M⁺ loss of H₂O)⁺.

Step 4: 4-{2-[(R)-2-((S)-(E)-5-Cyclopropyl-3-hydroxy-pent-1-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl}-butyric acid methyl ester



[000114] 6R-(5-Cyclopropyl-3S-hydroxy-pent-1E-enyl)-1-(2-hydroxyethyl)-piperidin-2-one from step 3 (328 mg, 1.23 mmol) was dissolved in tetrahydrofuran (10 mL) and cooled to -20 °C under Argon. This solution was sequentially treated with triethylamine (0.21 mL, 1.48 mmol) and methanesulfonyl chloride (0.095 mL, 1.23 mmol) which resulted in a suspension. In a separate vessel, a solution of anhydrous methanol (1 mL) and anhydrous tetrahydrofuran (5 mL) under an argon atmosphere was treated with potassium *t*-butoxide (3.7 mL, 1 M tetrahydrofuran solution, Aldrich) and the slightly warm solution was stirred for 10 minutes. Thiobutyrolactone (0.26 mL, 3.1 mmol, Aldrich Chemical Co.) was added in one portion and stirred at ambient temperature for 10 minutes and the suspension of the mesylate was added via cannula to the potassium thiolate solution. The mixture was stirred for 18 hours at ambient temperature and then partitioned between aqueous ammonium chloride and ethyl acetate (4 x 25 mL). The combined organic extracts were stored over anhydrous sodium sulfate, and the volatiles were removed with a rotary evaporator. The resulting 4-{2-[(R)-2-((S)-(E)-5-cyclopropyl-3-hydroxy-pent-1-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl}-butyric acid methyl ester (98 mg, 0.25 mmol) was obtained following elution from silica gel chromatography with 4:1 ethyl acetate:hexane as an oil: ¹H NMR (300 MHz, CDCl₃) 5.58-5.64 (m, 2 H), 4.16-4.22 (m, 1 H), 4.02-4.07 (m, 1 H), 3.87-3.98 (m, 1 H), 3.68 (s, 3 H), 2.95-3.04 (m, 1 H), 2.63-2.76 (m, 2 H), 2.58 (t, *J* = 7.2 Hz, 2 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 2.34-2.41 (m, 2 H), 1.58-1.99 (m, 9 H), 1.22-1.30 (m, 2 H), 0.61-0.72 (m, 1 H), 0.40-0.47 (m, 2 H), 0.02-0.07 (m, 2 H).

Step 5: 4-{2-[(R)-2-((S)-(E)-5-Cyclopropyl-3-hydroxy-pent-1-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl}-butyric acid



5 [000115] A methanol (10 mL) solution of 4-{2-[(R)-2-((S)-(E)-5-Cyclopropyl-3-hydroxy-pent-1-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl}-butyric acid methyl ester from step (4, 98 mg, 0.25 mmol) was treated with sodium hydroxide (0.3 mL, 5 M aqueous) and stirred at ambient temperature for 3 hours. The volatiles were removed under a stream of nitrogen and the mixture was partitioned between water and ethyl ether. The aqueous layer was rendered acidic with hydrochloric acid (12 M aqueous) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts was stored over anhydrous sodium sulfate. 4-{2-[(R)-2-((S)-(E)-5-Cyclopropyl-3-hydroxy-pent-1-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl}-butyric acid (94 mg, 0.25 mmol) was obtained following filtration and removal of the volatiles as an oil: ¹H NMR (300 MHz, CDCl₃) 6.7 (br.s, 1 H), 5.58-5.63 (m, 2 H), 4.18-4.22 (m, 1 H), 4.02-4.07 (m, 1 H), 3.87-3.98 (m, 1 H), 2.98-3.08 (m, 1 H), 2.62-2.72 (m, 2 H), 2.59 (t, J = 6.9 Hz, 2 H), 2.36-2.49 (m, 4 H), 1.61-1.99 (m, 8 H), 1.22-1.30 (m, 2 H), 0.59-0.71 (m, 1 H), 0.40-0.46 (m, 2 H), 0.00-0.06 (m, 2 H); MS: m/z M⁺, 370.

20 [000116] Using the procedure of Example 2, , the following compounds of formula I were prepared with the following adaptations.

[000117] 4-{2-[(2R-[3R-(4'Chloro-2'methylbiphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl]-ethylsulfanyl) butyric acid was prepared by use of [2-(4'chloro-2'-methyl-biphen-3-yl)-2-oxo-ethyl] phosphonic acid dimethyl ester in step 2; in step 3, the enone was exposed to 1 atm of hydrogen gas with a catalytic amount of 10% Pd-C for 1.5 hours followed by treatment with (S)-2-methyl-CBS with borane-dimethyl sulfide at 0 °C: MS: m/z M⁺, 504 and 506.

[000118] 7-{2R-[3S-Hydroxy-4-(4-hydroxy-3-methyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid was prepared by the use of 3-[(4-hydroxy-3-methyl-

phenyl)-2-oxo-propyl] phosphonic acid dimethyl ester in step 2 and the exclusion of step 4: MS: m/z M^{+1} , 404.

[000119] 7-{2R-[3S-Hydroxy-4-(3-methoxymethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid was prepared by the use of 3-[(3-methoxymethyl-phenyl)-2-oxo-propyl] phosphonic acid dimethyl ester in step 2 and the exclusion of
5 step 4: MS: m/z M^{+1} , 418.

[000120] 7-{2R-[3S-Hydroxy-4-(4-hydroxy-3-isopropyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid was prepared by the use of 3-[(3-hydroxy-3-isopropyl-phenyl)-2-oxo-propyl] phosphonic acid dimethyl ester in step 2 and the exclusion of
10 step 4: MS: m/z M^{+1} , 432.

[000121] 4-(2-{2R-[3-Hydroxy-3-(1-phenylcyclopropyl)-prop-1E-enyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid was prepared by the use of 2-(phenylcyclopropyl)-2-oxo-ethyl] phosphonic acid dimethyl ester in step 2 and use of the combination cerium(III) chloride and sodium borohydride in step 3 instead of
15 the stereoselective "CBS" conditions: MS: m/z M^{+1} , 418.

[000122] 4-(2-{2R-[3R-3-Hydroxy-3-(trifluoromethyl-furan-2-yl)-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl) butyric acid was prepared by the use of 2-[(5-trifluoromethylfuran-2-yl)-2-oxo-ethyl] phosphonic acid dimethyl ester in step 2; in
20 step 3 the enone was exposed to 1 atm of hydrogen gas with a catalytic amount of 10% Pd-C for 1.5 hours followed by treatment with (S)-2-methyl-CBS with borane-dimethyl sulfide at 0 °C: MS: m/z M^{+1} , 438.

[000123] 4-(2-{2R-[3R-Hydroxy-3-(1-phenylcyclopropyl)-propyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid was prepared by the use of 2-[(phenylcyclopropyl)-2-oxo-ethyl] phosphonic acid dimethyl ester in step 2; in step 3 the enone was exposed
25 to 1 atm of hydrogen gas with a catalytic amount of 10% Pd-C for 1.5 hours followed by treatment with (S)-2-methyl-CBS with borane-dimethyl sulfide at 0° C: MS: m/z M^{+1} , 420

[000124] 4-(2-{2R-[3S-Hydroxy-4-(3-methoxymethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid was prepared by the use of 3-[(3-methoxymethyl-phenyl)-2-oxo-propyl] phosphonic acid dimethyl ester in step 2: MS:
30 m/z M^{+1} , 436.

[000125] 7-{2R-[3R-(4'-Hydroxy-2'-methylbiphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl} heptanoic acid was prepared by use of 2-(4'-hydroxy-2'-methyl-biphen-3-yl)-2-oxo-ethyl phosphonic acid dimethyl ester in step 2; in step 3, the enone was exposed to 1 atm of hydrogen gas with a catalytic amount of 10% Pd-C for 1.5 hours followed by treatment with (S)-2-methyl-CBS with borane-dimethyl sulfide at 0° C; and the exclusion of step 4: MS: m/z M^{+1} , 468.

[000126] 7-{2R-[3-Hydroxy-3-(4'-hydroxy-2'methylbiphenyl-3-yl)-prop-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid was prepared by the use of [2-(4'-hydroxy-2'-methyl-biphen-3-yl)-2-oxo-ethyl] phosphonic acid dimethyl ester in step 2; in step 3 the combination of cerium(III) chloride and sodium borohydride at 0° C; and the exclusion of step 4: MS: m/z M^{+1} , 466.

[000127] 7-(2-{2R-[3R-(4'-Hydroxy-2'methylbiphenyl-3-yl)-3-oxo-propyl]-6-oxo-piperidin-1-yl} heptanoic acid was prepared by the use of [2-(4'-hydroxy-2'-methyl-biphen-3-yl)-2-oxo-ethyl] phosphonic acid dimethyl ester in step 2; in step 3 the enone was exposed to 1 atm of hydrogen gas with a catalytic amount of 10% Pd-C for 2 hours; and the exclusion of step 4: MS: m/z M^{+1} , 466.

[000128] 4-{2-[2R-(5-Cyclobutyl-3S-hydroxy-pent-1E-enyl)-6-oxo-piperidin-1-yl]ethylsulfanyl} butyric acid was prepared by the use of (4-cyclobutyl-2-oxo-butyl) phosphonic acid dimethyl ester in step 2: MS: m/z M^{+1} , 384.

[000129] 4-(2-{2R-[3R-(3'-fluorophenoxy-phenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl) 3-methyl-butyric acid was prepared by use of [2-(3-fluorophenoxy-phen-3-yl)-2-oxo-ethyl] phosphonic acid dimethyl ester in step 2; in step 3, the enone was exposed to 1 atm of hydrogen gas with a catalytic amount of 10% Pd-C for 1.5 hours followed by treatment with (S)-2-methyl-CBS with borane-dimethyl sulfide at 0° C; and the use of methyl 4-mercapto-3-methyl butyrate in step 4 instead of -thiolactone: MS: m/z M^{+1} , 504.

[000130] 4-{2-[2R-(3-Hydroxy-4,4-dimethyl-oct-1E-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl} butyric acid was prepared by the use of (3,3-dimethyl-2-oxo-heptyl) phosphonic acid dimethyl ester in step 2; and the combination of cerium (III) chloride with sodium borohydride in step 3: MS: m/z M^{+1} , 400.

[000131] 7-{2R-[3-Hydroxy-3-(2,5-dimethylphenyl-3-yl)-prop-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid was prepared by the use of [2-(2,5-dimethyl-phen-3-

- 43 -

yl)-2-oxo-ethyl] phosphonic acid dimethyl ester in step 2; in step 3 the combination of cerium (III) chloride and sodium borohydride at 0° C; and the exclusion of step 4: MS: m/z M^{+1} , 388.

[000132] 7-[-2R-(3-Hydroxy-4-phenoxy-but-1E-enyl)-6-oxo-piperidin-1-yl] heptanoic acid was prepared by the use of (3-phenoxy-2-oxo-propyl) phosphonic acid dimethyl ester in step 2; in step 3 the combination of cerium (III) chloride and sodium borohydride at 0° C; and the exclusion of step 4: MS m/z M^{+1} , 390.

[000133] 7-{2R-[3-Hydroxy-3-(3'chloro-biphenyl-3-yl)-prop-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid was prepared by the use of [2-(3'-chloro-biphen-3-yl)-2-oxo-ethyl] phosphonic acid dimethyl ester in step 2; in step 3 the combination of cerium(III) chloride and sodium borohydride at 0° C; and the exclusion of step 4: MS: m/z M^{+1} , 470 and 472.

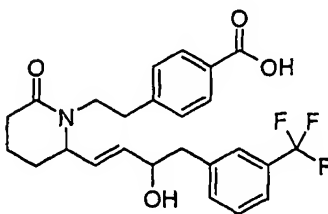
[000134] 7-{2R-[3R-(3'chloro-biphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl} heptanoic acid was prepared by the use of [2-(3'-chloro-biphen-3-yl)-2-oxo-ethyl] phosphonic acid dimethyl ester in step 2; in step 3 the enone was exposed to 1 atm of hydrogen gas with a catalytic amount of 10% Pd-C for 2 hours followed by the use the (S)-2-methyl-CBS with borane at 0° C; and the exclusion of step 4: MS: m/z M^{+1} , 472 and 474.

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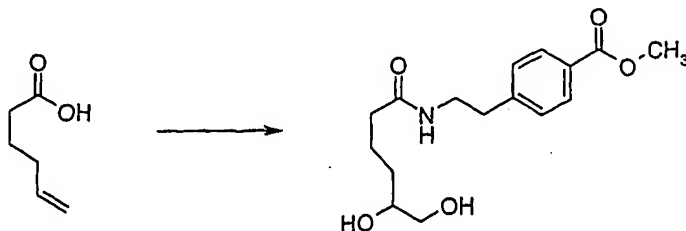
EXAMPLE 3

4-(2-(2-[3-Hydroxy-4-(3-trifluoromethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl)-ethyl) benzoic acid

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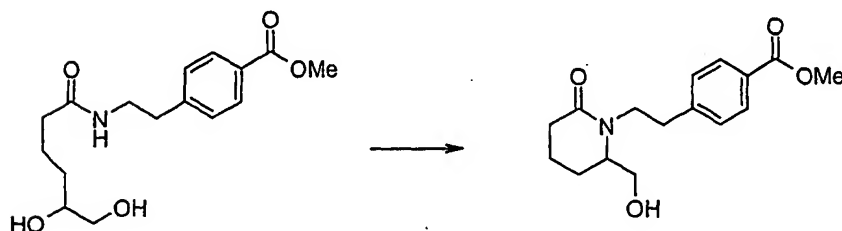


Step 1: 4-[2-(5,6-Dihydroxy-hexanoylamino)-ethyl] benzoic acid methyl ester.



[000135] A N,N-dimethylformamide (110 mL) solution of 5-hexenoic acid (8.45 g, 73.8
5 mmol, Aldrich) was treated with carbonyl diimidazole (12 g, 74 mmol) was heated to
50° C for 3 hours. The solution was cooled, treated with diisopropylethyl amine
(18.4 mL, 105 mmol) and methyl 4-(2-aminoethyl)benzoate (12.6 g, 70.3 mmol,
prepared according to T. Takemoto, et al. European Patent Application 0544205 to
Ajinomoto Co.), and heating resumed at 50 for 3 additional hours. The mixture was
10 partitioned between water (400 mL) and ethyl acetate (3 x 150 mL). The combined
organic extracts was washed with 1 M HCl, saturated NaHCO₃, and brine and stored
over anhydrous MgSO₄. The extract was filtered and the volatiles were removed in
vacuo. A solid (11.4 g) was obtained and was used directly dissolved in acetone (440
mL) and water (10 mL). This solution was treated with N-methyl morpholine N-
15 oxide (5.35 g, 45.7 mmol), osmium tetroxide (approx. 20 mg), and heated to reflux
for 3 hours. The alkene had been consumed by TLC and the mixture was cooled and
treated with aqueous solution on sodium bisulfite and rendered acidic with 1 M
aqueous HCl. 4-[2-(5,6-Dihydroxy-hexanoylamino)-ethyl] benzoic acid methyl ester
(12.85 g) was obtained as solid following extraction with chloroform (3 x 200 mL),
20 storage over anhydrous sodium sulfate, removal of the volatiles, and recrystallization
from ethyl acetate and a minor volume of methanol.

Step 2: 4-[2-(2-Hydroxymethyl-6-oxo-piperdin-1-yl)-ethyl] benzoic acid methyl ester



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[000136] A 0° C dichloromethane (170 mL) and DMF (35 mL) solution of 4-[2-(5,6-dihydroxy-hexanoylamino)-ethyl] benzoic acid methyl ester (7.4 g) was treated with 2,6-lutidine (9.1 mL), and t-butyldimethylsilyl trifluoromethanesulfonate (5.5 mL) and then stirred overnight. The mixture was partitioned between aqueous sodium bicarbonate and ethyl acetate (3 x 150 mL). The desired primary silyl ether (5.8 g) was isolated, following drying and evaporation of the volatiles with rotary evaporator, by silica gel chromatography elution with 2:1 hexanes:ethyl acetate. The ether (5.85 g) was dissolved in dichloromethane (50 mL) and triethyl amine (3.85 mL) and cooled to 0° C under an Argon atmosphere. The solution was treated with methanesulfonyl chloride (1.5 mL, 19.3 mmol) and stirred for 30 minutes, whereupon it poured into aqueous sodium bicarbonate. The desired secondary sulfonate (6.6 g) was obtained following extraction with dichloromethane (3 x 30 mL), drying over anhydrous sodium sulfate and removal of the volatiles in vacuo and used directly in the next operation. The crude secondary sulfonate (6.6 g, 13.2 mmol) was dissolved in anhydrous toluene (106 mL) at ambient temperature under Argon and treated with potassium t-butoxide (1 M, THF solution from Aldrich). After 2 hours, the brown mixture was partitioned between aqueous ammonium chloride and ethyl acetate (4 x 50 mL) and the combined organic extracts was stored over anhydrous sodium sulfate. The desired lactam (1.79 g, 4.6 mmol) was isolated by silica gel chromatography (eluent: 4:1 hexanes: ethyl acetate) and directly dissolved in tetrahydrofuran (23 mL). The solution was treated with tetrabutylammonium fluoride hydrate (1.74 g, 5.5 mmol) and stirred at rt for 1 hour. 4-[2-(2-Hydroxymethyl-6-oxo-piperdin-1-yl)-ethyl] benzoic acid methyl ester (1.055 g) was

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obtained following filtration through a pad of silica, washed with 1:1 ethyl acetate: hexane.

5 [000137] 4-(2-{2-[3-Hydroxy-4-(3-trifluoromethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl}-ethyl) benzoic acid was prepared from 4-[2-(2-hydroxymethyl-6-oxo-piperidin-1-yl)-ethyl] benzoic acid methyl ester according to Example 2 by employing 4-[(3-trifluoromethyl-phenyl)-2-oxo-butyl] phosphonic acid dimethyl ester (prepared according to Preparation 2) in step 2, and sodium borohydride in step 3, and excluding step 4: MS: m/z M^{+1} , 462.

10 [000138] According to Example 3, 4-(2-{2-[3-(4'chloro-2'-methyl-biphen-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl}-ethyl) benzoic acid was prepared with the following changes. In step 2, the [3-(4'chloro-2'-methyl-biphen-3-yl)-2-oxo-propyl] phosphonic acid dimethyl ester (prepared according to Preparation 2) was used, in step 3 the double was reduced under 1 atm hydrogen gas at ambient temperature with a catalytic amount of 10% Pd-C in ethyl acetate followed by treatment with sodium borohydride, and step 4 was excluded: MS: m/z M^{+1} , 507 and 509.

EXAMPLE 4

Formulations

20 [000139] Pharmaceutical preparations for delivery of the subject compounds by various routes are formulated as shown in the following Tables. "Active ingredient" or "Active compound" as used in the Tables means one or more of the Compounds of Formula I.

Composition for Oral Administration

Ingredient	% wt./wt.
Active ingredient	20.0%
Lactose	79.5%
Magnesium stearate	0.5%

[000140] The ingredients are mixed and dispensed into capsules containing about 100 mg each; one capsule would approximate a total daily dosage.

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Composition for Oral Administration

Ingredient	% wt./wt.
Active ingredient	20.0%
Magnesium stearate	0.5%
Crosscarmellose sodium	2.0%
Lactose	76.5%
PVP (polyvinylpyrrolidone)	1.0%

[000141] The ingredients are combined and granulated using a solvent such as methanol. The formulation is then dried and formed into tablets (containing about 20 mg of active compound) with an appropriate tablet machine.

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Composition for Oral Administration

Ingredient	Amount
Active compound	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g

Ingredient	Amount
Propyl paraben	0.05 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 ml

[000142] The ingredients are mixed to form a suspension for oral administration.

Parenteral Formulation

Ingredient	% wt./wt.
Active ingredient	0.25 g
Sodium Chloride	qs to make isotonic
Water for injection	100 ml

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[000143] The active ingredient is dissolved in a portion of the water for injection. A sufficient quantity of sodium chloride is then added with stirring to make the solution isotonic. The solution is made up to weight with the remainder of the water for injection, filtered through a 0.2 micron membrane filter and packaged under sterile conditions.

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Suppository Formulation

Ingredient	% wt./wt.
Active ingredient	1.0%
Polyethylene glycol 1000	74.5%

Polyethylene glycol 4000	24.5%
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[000144] The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

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Topical Formulation

Ingredients	grams
Active compound	0.2-2
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. 100

[000145] All of the ingredients, except water, are combined and heated to about 60°C with stirring. A sufficient quantity of water at about 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. about 100 g.

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Nasal Spray Formulations

[000146] Several aqueous suspensions containing from about 0.025-0.5 percent active compound are prepared as nasal spray formulations. The formulations optionally contain inactive ingredients such as, for example, microcrystalline cellulose, sodium carboxymethylcellulose, dextrose, and the like. Hydrochloric acid may be added to adjust pH. The nasal spray formulations may be delivered via a nasal spray metered pump typically delivering about 50-100 microliters of formulation per actuation. A typical dosing schedule is 2-4 sprays every 4-12 hours.

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EXAMPLE 5

Functional activity of EP₄ (or EP₂) receptor by a Luciferase Assay

5 a. Generation of stably transfected EP4-luciferase clones

[000147] Prostanoid receptor EP4 cDNA corresponding to the full-length coding sequence was subcloned into the appropriate sites of the mammalian expression vector pcDNA 3.1(+)/Zeo (Invitrogen). In addition, the sequence containing CAMP responsive element (CRE) and luciferase gene was cloned to a pXP1 vector. The co-
10 transfection to the CHO cells with EP4R containing pcDNA and CRE-luciferase containing pXP1 were carried out with a DNA ratio of 5 to 1 by Fugene (Roche Molecular) in a F-12 media (Gibco) supplemented with 10% heat inactivated fetal Bovine Serum (Gibco). Three days after the transfection, the culture was replace with fresh media containing Zeocin. The culture was maintained for one month until
15 stable clones were generated.

 b. c-AMP dependent luciferase gene assay

[000148] The functional activity of an EP4 agonistic ligand upon its binding to the receptor was measured by the production of intra-cellular c-AMP. Here the level of
20 c-AMP was measured indirectly by the translation of a reporter gene, luciferase in the EP4-luciferase clones. The cells of EP4-luciferase clone were subcultured in 200 ul of F12 (Gibco, BRL) media containing 10% FBS(Gibco, BRL), and 25 mM Hepes to 96-well plates (Packard) at the density of 40,000 cells/well. After an overnight culture at 37°C, 5% CO₂, 95% air, the culture media was removed in the next morning. The
25 cells were washed twice with 100 ul of Hanks buffer, and re-furnished with 90 ul of F12 media containing 0.1% BSA. After pre-incubation of the culture for one and half to three hours at 37°C, 5% CO₂, 95% air, 10 ul of compounds of interest at 10 X of desired concentration were added to culture and the incubation at 37 °C was continued for another three hours. 0.1 uM of PGE₂ as a full agonist control was
30 routinely included to each assay to determine the maximal stimulation of luciferase mediated through EP4 receptor.

[000149] At the end of incubation, the culture media was dumped and blotted to dry.
The plate was then ready to assay for luciferase.

c. Quantitation of luciferase activity

5 [000150] An assay kit, LucLite, purchased from Packard was used to quantitate luciferase activity. 30 minutes prior to end of incubation, LucLite substrate and substrate buffer (Packard) were allowed to equilibrate to room temperature. The substrate was dissolved in the substrate buffer and mixed by inversion. Equal volumes of
10 Dulbecco's Phosphate Buffered Saline (DPBS, Gibco BRL) containing 1mM MgCl₂ and 1 mM CaCl₂ were then mixed with the reconstituted substrate solution for use in the next step. 100 ul of the mixed solution was added to each well of the 96-well plate. The plate was shaken at 300 rpm on plate shaker for 3 min. The plate cover was removed and replaced with plate sealer (Packard) for counting in a scintillation counter. The EC₅₀ of a compound was then determined by a four-parameter
15 curvefit program of KaleidaGraph. Compounds of Formula I showed activity using the above assay.

EXAMPLE 6

Competitive Binding Assay of [³H]PGE₂ to rEP₁, rEP₂, rEP₃ and rEP₄ Receptor

20 a. Cell Culture and Transfections

[000151] Stably transfected cells expressing EP3 were grown in F-12 media (GIBCO) supplemented with 10% heat inactivated certified Fetal Bovine Serum (GIBCO) and pelleted. Prostanoid receptor EP2 or EP4 cDNA corresponding to the full-length
25 coding sequence was subcloned into the appropriate sites of the mammalian expression vector pcDNA 3.1(+)/Zeo (Invitrogen). Transfection-scale quantities of the vector were prepared using the Qiagen Endo-Free Plasmid Maxi Kit and transfected into COS-7 cells using FuGene 6 (Roche Molecular) according to the manufacturer's instructions (Roche). COS-7 cells were grown in DMEM (GIBCO) supplemented with 10% heat inactivated certified Fetal Bovine Serum (GIBCO) and
30 Gentamicin (GIBCO), and were harvested 72 hours after transfection. Cells were

pelleted by centrifugation, washed with PBS (GIBCO), repelleted, then flash-frozen in dry-ice/Ethanol or used directly for membrane preparation.

b. Membrane Preparation

5 [000152] All procedures for membrane preparation were performed at 4° C. Prostanoid
receptor-transfected COS-7 cells or stably transfected CHO cells were homogenized
in assay buffers (see recipe, below) using a Polytron homogenizer (Brinkman) and
centrifuged at 48,000 x g for 30 minutes. Pellets were resuspended in assay buffer and
resuspended by sonication using a Branson sonifier. Protein concentration was
10 determined using the BioRad DC Protein Assay following the manufacturer's
directions and stored at -80° C.

c. Prostanoid Receptor Binding Assays

15 [000153] Methods for competitive affinity binding assays of EP2 , EP3 and EP4 were
derived from those described in M. Abramovitz et al, "The utilization of recombinant
prostanoid receptors to determine the affinities and selectivities of prostaglandins and
related analogs" Biochimica et Biophysica Acta 1483 (2000) 285-293. Binding assays
were performed in a final incubation volume of 0.2 mL in the following assay buffers:
20 mM HEPES, 1 mM EDTA, and 10 mM MgCl₂ (pH 7.4) (EP3) or 10 mM MES, 10
20 mM MnCl₂, and 1 mM EDTA (pH to 6.0 with NaOH) (EP2 and EP4) and
radioligand {2.25 nM (EP3) or 2.5 nM (EP2) [3H]-PGE₂ (200 Ci/mmol, NEN)}.
Reactions were initiated by addition of membrane protein (approximately 50
ug/reaction for EP3, 100 ug for EP2 and EP4). Dimethylsulfoxide (Sigma)
concentration was kept constant at 1% (v/v) in all incubations, and compounds were
25 assayed at final concentrations of 100 uM-0.3 nM. Non-specific binding was
determined in the presence of 10 μ M of non-radioactive PGE₂ (Cayman Chemical).
Incubations were conducted for 60 minutes at 30° C (EP3) or 45 minutes at 23 C
(EP2 and EP4). Incubations were terminated by rapid filtration through a 96-well
Unifilter GF/B (Packard) (prewetted in 10 mM MES, 0.01% BSA, pH 6.0 for EP2) at
30 4 C using a Filtermate 196 96-well semi-automated cell harvester (Packard). The
filters were washed with 3-4 mL of wash buffer (20 mM HEPES pH 7.4 for EP3, 10
mM MES, 0.01% BSA, pH 6.0 for EP2 and EP4), dried for at least 1 hour at room
temperature, and the residual radioactivity bound to the individual filters determined

by scintillation counting with addition of 37.5 uL of Microscint 20 (Packard) using a Packard TopCount Microplate Scintillation Counter. Statistics of binding were determined using Prism v 3.0 software (GraphPad). Compounds of Formula I showed activity using the above assays.

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EXAMPLE 7

Bone Mass Density Assay

[000154] The compounds of this invention may be evaluated for their effect on bone mass in ovariectomized rats.

10 [000155] Adult Sprague-Dawley or Wistar Hanover female rats are either sham operated or ovariectomized by Charles River. On receipt, rats are housed in pairs in an environmentally controlled room and acclimatized for at least one week. Animals are pair fed while were housed on site.

15 [000156] Test compound are administered subcutaneously once a day started from 20 days post surgery for 5 weeks in 10% EtOH/saline or 20 mM phosphate buffer.

20 [000157] Before the treatment and at the end of the treatment, rats are scanned using High Resolution Software Package on a Hologic QDR-4500 Bone Densitometer to measure the bone mineral density (BMD). Scans are then analyzed using regions of interest, as designated below: whole femur, proximal femur, femur diaphysis, distal femur, distal femur metaphysis, proximal tibia, proximal tibia metaphysis, L2-L4 vertebrae, L5 vertebrae.

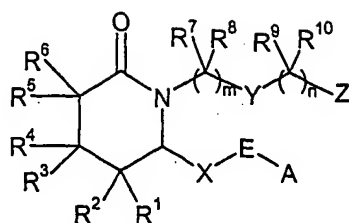
25 [000158] For a verification of the effect of ovariectomy on bone mass, the sham and OVX of like vehicle groups are compared using a students t-test. The OVX groups are compared by one way analysis of variance (ANOVA), followed by Fisher's LSD to compare each treatment group to vehicle when the overall effect was statistically significant. The data could be ranked prior to the above analysis and corresponding non-parametric analysis is performed (Wilcoxon rank-sum test or Kruskal-Wallis).

30 [000159] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the

true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

CLAIMS

1. A compound of the Formula I



I

wherein:

m is from 1 to 4;

n is from 0 to 4;

A is alkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, cycloalkylalkyl, or aryloxyalkyl;

E is -CHOH- or -C(O)-;

X is -(CH₂)₂- or -CH=CH-;

Y is -CH₂-, -CH=CH-, arylene, heteroarylene, -O-, -S(O)_p- where p is from 0 to 2,
or -NR_a- where R_a is hydrogen or alkyl;

Z is -CH₂OH, -CHO, tetrazole-5-yl or -COOR_b where R_b is hydrogen or alkyl; and

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ each independently are hydrogen or
alkyl;

or a pharmaceutically acceptable salt, solvate, prodrug, single isomer or racemic or
non-racemic mixture of isomers thereof.

2. The compound of claim 1, wherein E is -CHOH-.

3. The compound of claim 1 or claim 2, wherein Z is -COOR_b.

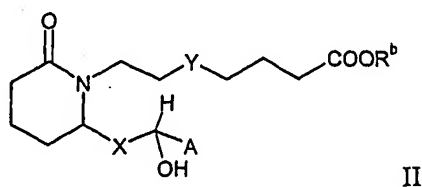
4. The compound according to any of claims 1 to 3, wherein Y is -CH₂-.

5. The compound according to any of claims 1 to 3, wherein Y is -S(O)_p- and p is 0.

6. The compound according to any of claims 1 to 3, wherein Y is arylene.

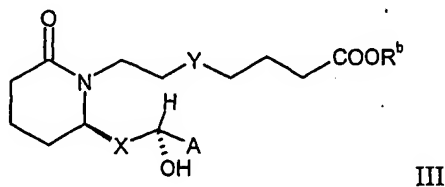
7. The compound according to any of claims 1 to 6, wherein X is -CH=CH-.

8. The compound according to any of claims 1 to 6, wherein X is $-(CH_2)_2-$.
9. The compounds according to any of claims 1 to 8, wherein A is independently selected from the group consisting of alkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, cycloalkylalkyl and aryloxyalkyl.
10. The compound according to any of claims 1 to 9, wherein A is alkyl.
11. The compound according to any of claims 1 to 9, wherein A is aryl.
12. The compound according to any of claims 1 to 9, wherein A is heteroaryl.
13. The compound according to any of claims 1 to 9, wherein A is arylalkyl.
14. The compound according to any of claims 1 to 9, wherein A is arylcycloalkyl.
15. The compound according to any of claims 1 to 9, wherein A is cycloalkylalkyl.
16. The compound according to any of claims 1 to 9, wherein A is aryloxyalkyl.
17. The compound according to any of claims 1 to 16, wherein said compound is of the Formula II



wherein Y is $-CH_2-$ or $-S-$, and A, X and R^b are as defined any of claims 1 to 16.

18. The compound of claim 17, wherein said compound is of the Formula III:



wherein A, X, Y and R^b are as defined in any of claims 1 to 16.

19. The compound of claim 18, wherein X is $-\text{CH}=\text{CH}-$.
20. The compound of claim 18 or 19 wherein Y is arylene.
21. The compound of claim 1, wherein said compound is selected from:
 - w. 4-{2-[(R)-2-((S)-(E)-5-Cyclopropyl-3-hydroxy-pent-1-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl}-butyric acid;
 - x. 4-(2-{2R-[3R-(4'Chloro-2'methylbiphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl) butyric acid;
 - y. 7-{2R-[3S-Hydroxy-4-(4-hydroxy-3-methyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic;
 - z. 7-{2R-[3S-Hydroxy-4-(3-methoxymethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid;
 - aa. 7-{2R-[3S-Hydroxy-4-(4-hydroxy-3-isopropyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid;
 - bb. 4-(2-{2R-[3-Hydroxy-3-(1-phenylcyclopropyl)-prop-1E-enyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid;
 - cc. 4-(2-{2R-[3R-3-Hydroxy-3-(trifluoromethyl-furan-2-yl)-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl) butyric;
 - dd. 4-(2-{2R-[3R-Hydroxy-3-(1-phenylcyclopropyl)-propyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid ;
 - ee. 4-(2-{2R-[3S-Hydroxy-4-(3-methoxymethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl}ethylsulfanyl) butyric acid;
 - ff. 7-{2R-[3R-(4'-Hydroxy-2'-methylbiphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl} heptanoic acid;
 - gg. 7-{2R-[3-Hydroxy-3-(4'-hydroxy-2'methylbiphenyl-3-yl)-prop-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid;
 - hh. 7-(2-{2R-[3R-(4'-Hydroxy-2'methylbiphenyl-3-yl)-3-oxo-propyl]-6-oxo-piperidin-1-yl} heptanoic acid;
 - ii. 4-{2-[2R-(5-Cyclobutyl-3S-hydroxy-pent-1E-enyl)-6-oxo-piperidin-1-yl]ethylsulfanyl} butyric acid;
 - jj. 4-(2-{2R-[3R-(3'-fluorophenoxy-phenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl}-ethylsulfanyl) 3-methyl-butyric acid;
 - kk. 4-{2-[2R-(3-Hydroxy-4,4-dimethyl-oct-1E-enyl)-6-oxo-piperidin-1-yl]-ethylsulfanyl} butyric acid;
 - ll. 7-{2R-[3-Hydroxy-3-(2,5-dimethylphenyl-3-yl)-prop-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid;
 - mm. 7-[-2R-(3-Hydroxy-4-phenoxy-but-1E-enyl)-6-oxo-piperidin-1-yl] heptanoic acid;

- nn. 7-{2R-[3-Hydroxy-3-(3'chloro-biphenyl-3-yl)-prop-1E-enyl]-6-oxo-piperidin-1-yl} heptanoic acid;
oo. 7-{2R-[3R-(3'chloro-biphenyl-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl} heptanoic acid;
5 pp. 4-(2-{2-[3-Hydroxy-4-(3-trifluoromethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl}-ethyl) benzoic acid;
qq. 4-(2-{2-[3-Hydroxy-4-(3-trifluoromethyl-phenyl)-but-1E-enyl]-6-oxo-piperidin-1-yl}-ethyl) benzoic acid; and
rr. 3, 4-(2-{2-[3-(4'chloro-2'-methyl-biphen-3-yl)-3-hydroxy-propyl]-6-oxo-piperidin-1-yl}-ethyl) benzoic acid.
10
22. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in any of claims 1 to 21 in admixture with at least one suitable carrier diluent or excipient.
23. A method of treatment of a disease in a mammal treatable by administration of a selective EP4 prostaglandin agonist comprising administration to the mammal a therapeutically effective amount of a compound as defined in any of claims 1 to 21.
15
24. The method of claim 23, wherein the disease is associated with bone disorders.
25. The method of claim 24, wherein the disease is osteoporosis.
26. The compounds of any of claims 1 to 21 for use in therapy.
- 20 27. A use of a compound as defined in any of claims 1 to 21 for the manufacture of medicaments.
28. The use of a compound as defined in any of claims 1 to 21 for the manufacture of medicaments for the treatment of bone disease.
29. The use as defined in claim 28, wherein the disease is osteoporosis.
- 25 30. A process for the production of compounds as defined in claims 1 to 21 comprising the steps described in schemes 1 to 3.
31. The invention as hereinbefore defined.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/000008

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/76

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BE 841 165 A (SYNTEX) 27 October 1976 (1976-10-27) cited in the application page 3, line 25 -page 4, line 6	1-31
Y	AU 512 960 B (BEECHAM GROUP LTD) 6 November 1980 (1980-11-06) page 4, line 1 -page 5, line 5	1-31
Y	BIAGGIO, F.C.; BARREIRO E.J.: J. HETEROCYCL. CHEM., vol. 26, 1989, pages 725-728, XP002278225 the whole document	1-31
P, Y	WO 03/007941 A (HOFFMANN LA ROCHE) 30 January 2003 (2003-01-30) the whole document	1-31
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- *8* document member of the same patent family

Date of the actual completion of the international search

27 April 2004

Date of mailing of the international search report

13/05/2004

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Zellner, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/000008

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 241 050 A (HISAMITSU PHARMACEUTICAL CO) 14 October 1987 (1987-10-14) the whole document -----	1-31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/000008

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of Box II.1

Although claims 23-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/EP2004/000008

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
BE 841165 A	27-10-1976	BE 841165 A1 DE 2618341 A1 FR 2309222 A1 JP 51143663 A NL 7604330 A	27-10-1976 11-11-1976 26-11-1976 10-12-1976 01-11-1976
AU 512960 B	06-11-1980	AU 512960 B2 AU 2995177 A	06-11-1980 26-04-1979
WO 03007941 A	30-01-2003	CA 2451393 A1 WO 03007941 A1 EP 1408961 A1 US 2003064964 A1	30-01-2003 30-01-2003 21-04-2004 03-04-2003
EP 0241050 A	14-10-1987	JP 1914458 C JP 6043390 B JP 62238261 A AT 81505 T AU 601402 B2 AU 7020787 A CA 1336597 C CN 87100666 A ,B CN 1060287 A ,B CN 1060465 A ,B DE 3782182 D1 DE 3782182 T2 EP 0241050 A2 ES 2046196 T3 GR 3006768 T3 WO 8706226 A2 KR 9100164 B1 KR 9100478 B1 KR 9100479 B1 KR 9100480 B1 SU 1748644 A3 SU 1750422 A3 SU 1750423 A3 US 4882359 A	23-03-1995 08-06-1994 19-10-1987 15-10-1992 13-09-1990 09-11-1987 08-08-1995 21-10-1987 15-04-1992 22-04-1992 19-11-1992 25-02-1993 14-10-1987 01-02-1994 30-06-1993 22-10-1987 21-01-1991 25-01-1991 25-01-1991 25-01-1991 15-07-1992 23-07-1992 23-07-1992 21-11-1989

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